EVALUATION OF PHOSPHORYLATED CERVICAL INSULIN LIKE GROWTH FACTOR BINDING PROTEIN FOR THE PREDICTION OF PRETERM DELIVERY

Dissertation submitted to **Dr.M.G.R Medical University**

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In partial fulfillment of the Regulations

for the award of the degree of

M.S in Obstetrics and Gynaecology

GOVERNMENT STANLEY MEDICAL COLLEGE
Chennai 600001

April - 2015

CERTIFICATE

This is to certify that this dissertation ***EVALUATION OF PHOSPHORYLATED CERVICAL INSULIN LIKE GROWTH FACTOR BINDING PROTEIN FOR THE PREDICTION OF PRETERM DELIVERY*** submitted by Dr.Vidhya Jayashree.K, appearing for Part II MS, Branch II Obstetrics and Gynaecology Degree Examination in April 2015 is a bonafide record of the work done by her under my direct guidance and supervision as per the rules and registration of the TamilNadu Dr.M.G.R Medical University, Chennai, Tamil Nadu, India. I forward this dissertation to the Tamil Nadu Dr.M.G.R Medical University Chennai, India.

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DECLARATION

I Dr.K.Vidhya Jayashree, solemnly declare that the dissertation titled **Evaluation of phosphorylated cervical insulin like growth factor binding protein for the prediction of preterm delivery** is a bonafide work done by me at R.S.R.M. Lying in hospital Stanley Medical College and Chennai during September 2013-September 2014 under the guidance and supervision of Prof. .Dr.V.KALAIVANI M.D., D.G.O. Professor and Head of the department of Obstetrics and Gynaecology.

This dissertation is submitted to the Tamil Nadu Dr.M.G.R Medical University in partial fulfilment of University rules and regulation for the award of M.S.Degree (Branch-II) in Obstetrics and Gynaecology.

Place :Chennai **Dr.VIDHYA JAYASHREE.K**

Date:

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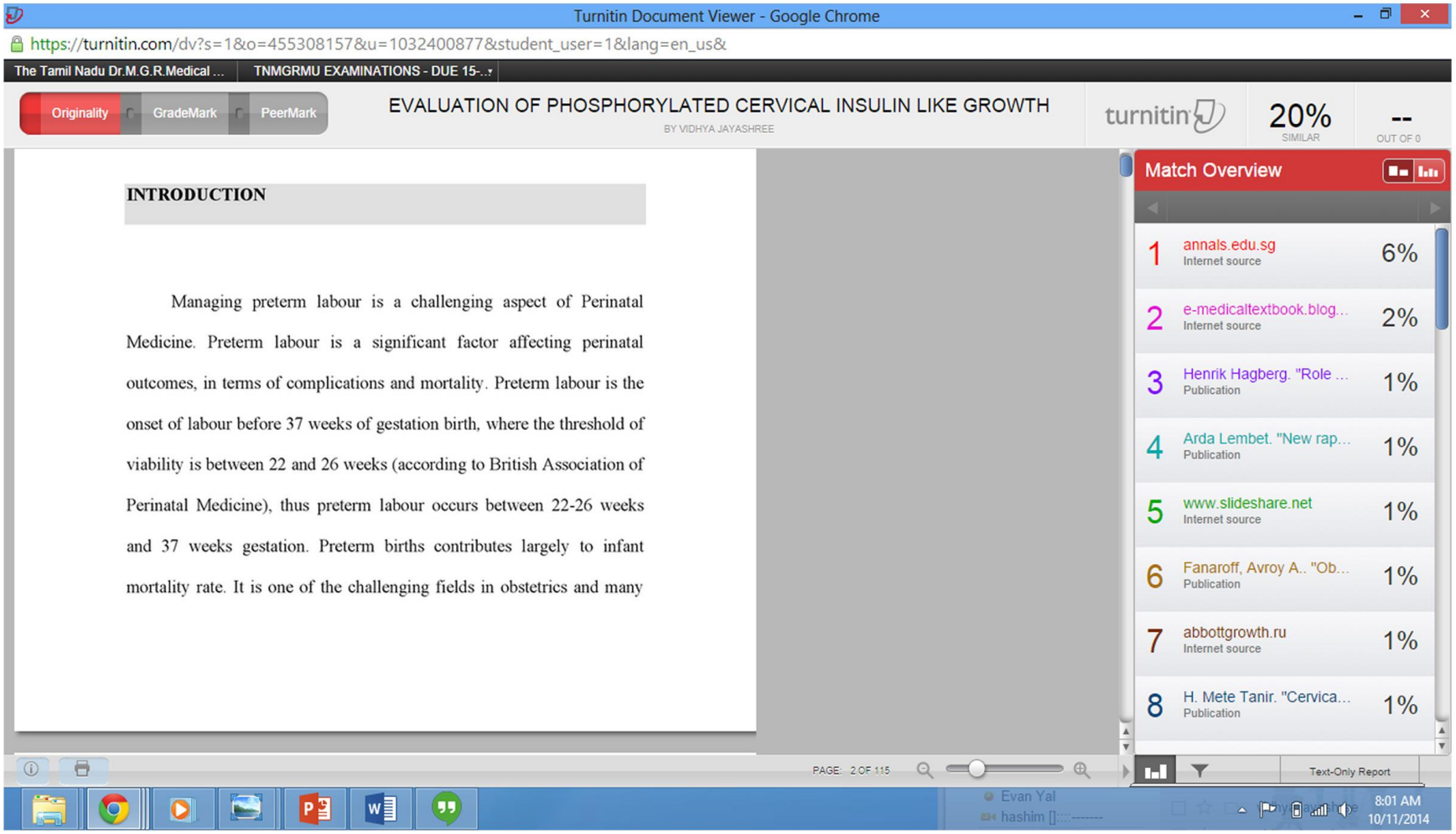
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INTRODUCTION
Managing preterm labour is a challenging aspect of Perinatal Medicine. Preterm labour is a significant factor affecting perinatal outcomes, in terms of complications and mortality. Preterm labour is the onset of labour before 37 weeks of gestation birth, where the threshold of viability is between 22 and 26 weeks (according to British Association of Perinatal Medicine), thus preterm labour occurs between 22-26 weeks and 37 weeks gestation. Preterm births contributes largely to infant mortality rate. It is one of the challenging fields in obstetrics and many
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INTRODUCTION

Managing preterm labour is a challenging aspect of Perinatal Medicine. Preterm labour is a significant factor affecting perinatal outcomes, in terms of complications and mortality. Preterm labour is the onset of labour before 37 weeks of gestation birth, where the threshold of viability is between 22 and 26 weeks (according to British Association of Perinatal Medicine), thus preterm labour occurs between 22-26 weeks and 37 weeks gestation. Preterm births contributes largely to infant mortality rate. It is one of the challenging fields in obstetrics and many new tests and drugs are under trial to improve the outcomes of preterm labour.

Preterm delivery constitutes about 11% births in U.S and more in developing countries. Preterm delivery is on the raise due to medical complications, increase in assisted reproductive techniques, stress and other reasons. Infant mortality rate also depends on the period of gestation when preterm labour occurs.

In the developed world most hospitals are well equipped with neonatal care for preterm infants. In developing countries like India neonatal

support for preterm infants are yet to be opened in most hospitals. This warrants an early and correct diagnosis of preterm labour and timely referral to higher centres for preterm care and avoid unnecessary referrals. Preterm birth continues to be a leading cause of neonatal morbidity and mortality. Absence of a reliable screening method to confirm preterm labour is another challenging factor.

Cervicovaginal phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) is one of the major proteins of the decidualised endometrium. Concentration in the amniotic fluid is 100 to 1000 times higher than that in the serum. Amniotic fluid contains the non-phosphorylated form and the lesser phosphorylated form. Decidua is abundant in phosphorylated insulin-like growth factor binding protein-1 a highly phosphorylated isoform of IGFBP-1.It is detected in cervicovaginal secretions before the onset of labour due to the detachment of the foetal membranes from the decidua.

Cervicovaginal detection of phIGFBP-1has been proposed as a reliable predictor of impending preterm delivery.

This study aims to **evaluate the prediction of preterm labour with the detection of cervical phosphorylated insulin like growth factors**.

LITERATURE REVIEW

DEFINITIONS

Preterm Labour

WHO defines Preterm labour as "*the commencement of regular uterine contractions, between viability and 37 weeks of gestation, along with cervical effacement and dilatation.*

Threshold of viability

Preterm delivery before 26 weeks or babies weighing less than 750 gm are at the current threshold of viability according to ACOG 2002, 2008 and suffer from many problems like medical, social. According to American Academy of Paediatrics current guidelines it is not necessary to resuscitate infants born prior to 23 weeks or those weighing less than 400 gm. Infants born at 22, 23, 24, or 25 weeks are considered to be under threshold due to immature organ systems. These infants are at higher risk for ischemic brain injuries as active brain development occurs during second and third trimester.

According to Tyson and associates (2008) factors improving the prognosis of preterm infants at the threshold of viability were singleton

pregnancy, female gender, steroids given for foetal lung maturation, and higher gestational age.

In 2008 Mc Intire and Leveno reported that idiopathic natural preterm labour or premature tear of membranes constituted 80% of late preterm births and the rest of 20% was constituted by complications like hypertension, placental abnormalities.

REASONS FOR PRETERM DELIVERY

About 40-45% of preterm labour occurs spontaneously and 30% because of rupture of membranes (preterm) , and the rest 30-35% are induced preterm labours. One of the major reasons for preterm include multiple pregnancies. Etiology of preterm labour is multifactorial. Some of the factors attributing to preterm are:-

- **Delivery for maternal or fetal indications**
- **Idiopathic preterm premature rupture of membranes**
- **High order births**
- **Uterine anomalies**
- **Foetal anomalies**
- **Genital tract infections**
- **Placental causes**

- **Foetal causes**
- **Unexplained reasons**

Delivery for maternal or foetal indications:

Indicated preterm delivery is done for various reasons. One third of preterm delivery is iatrogenic indicated for maternal or foetal reasons. These include:

Maternal causes

- Preeclampsia
- Placenta previa
- Abruption
- Chronic hypertension
- Diabetes
- Renal disease
- Cardiac disease

Foetal causes

- Foetal distress

- Severe foetal growth restriction due to utero placental insufficiency
- Rh iso immunisation
- Severe oligohydramnios
- Congenital malformation.

Idiopathic preterm premature rupture of membranes

Preterm rupture of membranes may occur due to reduction of membrane strength or due to increased intrauterine pressure theoretically. The amniotic membranes is a connective tissue and any defect in synthesis, degradation or collagen quality can result in preterm rupture of membranes.

High order births

Multiple gestation constitutes about 12-15% of all preterm births. Multiple gestations cause over distention of uterus resulting in initiation of preterm labour, infection, preterm rupture of membranes.Early activation of CRH and the physiological pathway for parturition,and over distention mechanical force leading to activation of protein kinase Mitogen –activated protein kinases and increased expression of G

proteins that induce myometrium contractility are the proposed mechanisms of preterm labour.

Uterine Anomalies

Congenital anatomical abnormalities of uterus and cervix are seen in 1-3% of preterm births. They occur due to mullerian ducts defect and septate and bicornuate uterus are clinically significant. The rate of preterm delivery in these patients range about 16-20%. Overdistention of uterus caused by multiple gestation, polyhydramnios also contribute to preterm labour.

Cervical Abnormalities

About 5 % of preterm births are due to anatomical or physiological abnormalities of cervix. These include women exposed to diethylstilboestrol during intrauterine period, who had conisations or cervical surgeries.

Genital tract infections

Infection is one of the most common cause of preterm labour and responsible for 20-40% of all preterm cases. The most accepted mechanism is ascending infection. This theory suggests an occurrence of

break in the normal physiological barrier present between the vaginal flora and the products of conception. The vaginal bacteria ascend through the breech and colonise the decidua and chorion and then enters the amniotic fluid and the foetus. This is supported by the fact that organisms secluded from the amniotic fluid and the vagina are similar. The vaginal flora is separated by the cervix and the cervical mucus plug. Cervical changes and changes in mucus plug contribute to ascending infection. Common organisms include Chlamydia, group B streptococcus, trichomonas, Gonococcus. Repeated pelvic examination during pregnancy and sexual intercourse are also implicated.

According to Goldenberg and colleagues (2008b) these intrauterine infections trigger the innate immune system and activate preterm labour. These organisms initiate the release of inflammatory cytokines like tumour necrosis factor and interleukins which stimulates prostaglandins production which leads to uterine contractions there by leading to preterm labour.

Intra uterine infections – Chorioamnionitis

Acute chorioamnionitis diagnosis is clinical and is diagnosed by the presence of fever and 2 of the following features maternal or foetal tachycardia, bad smell of amniotic fluid, maternal leucocytosis, and

uterine tenderness. Labour in these patients occur as a protective mechanism.

Subclinical chorioamnionitis is an infection of the conceptus without clinical signs or symptoms of the disease. This condition occurs in preterm labour with ruptured membranes or incompetent cervix. Patients with subclinical chorioamnionitis present with uterine contractions. The diagnosis is by amniotic fluid analysis for Gram stain, white cell count, concentrations of interleukin 6, glucose, lactate dehydrogenase and cultures. The most common organisms isolated are Urea plasma urealyticum, Mycoplasma hominis, Fusobacterium species and Gardenella vaginalis.

The leukocyte count in amniotic fluid analysis WBC >12,000/mm3 or or left shift or bandemia (>9%) suggests chorioamnionitis. Concentration of glucose in amniotic fluid is also used as a method to diagnose chorioamnionitis. The best marker for chorioamnionitis is IL-6 concentration of greater than 7.9ng/ml in patients with ruptured membranes and more than 11.39 ng/ml in patients with intact membranes.

Extra uterine infections

Bacteria may acquire contact to the lower pole of the uterus though a normally functioning cervix, because of an increased number of virulent

pathogens in the vagina, where they activate inflammatory mediators that leads to cervical ripening and shortening. Many criteria and tests have been followed to diagnose bacterial vaginosis

1. Spiegel's criteria

Normal: Gram stain shows a predominance of Lactobacillus acidophilus (3+ or 4+), with or without Gardenella vaginalis

Bacterial vaginosis: Gram stain shows absent or decreased Lactobacillus acidophilus (zero to 2+) and mixed flora (gram-positive, gram-negative or gram-variable bacteria).

Lactobacillus acidophilus (large gram-positivebacilli)

Gardnerella vaginalis (small gram-variable rods)

Counting for the above bacterial morphotypes 0 = No morphotypes per oil-immersion field

1+ = Less than one morphotypes per oil-immersion field

2+ = One to five morphotypes per oil-immersion field

3+ = Six to 30 morphotypes per oil-immersion field

4+ = More than 30 morphotypes per oil-immersion field

2. Amsel's diagnostic criteria

- Thin, homogeneous discharge
- Vaginal pH > 4.5 three of four criteria must be met to diagnose bacterial vaginosis
- Positive "whiff" test
- "Clue cells" located on microscopy (highly significant criterion)

3. Nugent's criteria

Based on the examination of the four bacterial morphotypes, the interpretation of the Gram stain was interpreted based on a standardised criteria by Nugent et. al. It is the assessment of relative concentration of bacterial morphotypes characteristics of altered flora. According to Nugent's criteria, a score of 4-10, indicates abnormal vaginal flora.

According to Romero et al. (1988) 5-10% of preterm labour patients have an infection outside the uterus. Urinary tract infections also cause preterm labour. These infections provoke the synthesis of production of interleukins and TNF by the macrophages which in turn cause prostaglandin synthesis by the amnion which result in preterm labour. About 25% of patients with preterm labour have a urine analysis

suggestive of urinary tract infection. Group B streptococcus infection of the urinary tract has been related to preterm labour. The occurence of preterm labour has been reduced in patients treated against group B streptococcus infection.

Asymptomatic bacteriuria association with preterm labour is controversial (Kaaset al.1970). As reported by Romero et al., 1989 evidence support a relationship between asymptomatic bacteriuria and preterm labour.

Gingivitis is also associated with preterm labour (Jeffcoat et al., 2001) .The bacteria found in periodontal disease and those in placental culture of preterm labour patients are found to be similar. These bacteria spread through haematogenous route and colonise the uterus resulting in preterm labour. Contractility are the proposed mechanisms of preterm labour.

INFECTIONS ASSOCIATED WITH PRETERM DELIVERY	
GENITAL	Bacterial Vaginosis (BV) Group B streptococcus Chlamydia Mycoplasmas
INTRAUTERINE	Ascending (from genital tract) Trans placental (blood-borne) Trans fallopian (intraperitoneal) Iatrogenic (invasive procedures)
EXTRAUTERINE	Pyelonephritis Malaria Typhoid fever Pneumonia Listeria Asymptomatic bacteriuria

Placental causes

- Abnormal placentation
- Anatomical abnormalities
- Placenta praevia
- Abruption placenta

Abnormal placentation

Abnormal placentation has been implicated as one of the causes of preterm labour. Histological studies of placenta (Arias et al.,1993) in preterm labour shows some defect in spiral arteries development, spiral artery thrombosis, and the placenta are small and have calcifications, infarctions and fibrosis . Decrease in uteroplacental flow causes foetal growth retardation and hence account for low birth infants in preterm labour(Lackman et al., 2001). Studies have shown that patients with Doppler abnormalities in early gestation have higher incidence of pretermlabour. Abnormal morphology, implantation, and functions of placenta also result in preterm labour.

Anatomical abnormalities

Marginal insertion of cord, battledore placenta, circumvallate placenta are also associated with preterm labour.

Abruption placenta

Placental Abruption is an abnormal premature separation of a normally implanted placenta. There are different kinds of abruption, based on the extent and region of separation.

Abruption of the placenta may lead to preterm labour, through the thrombin release, which encourages myometrial contractions by protease-activated receptors. With placental abruption, there is no time for pre-ripening of the uterine cervix to occur, hence the preterm labour with chorioamnionitis is mostly quick, whereas those with placental abruption, is less. (Phillip R.Bennet, 2011).

Placenta Previa

Placenta Previa can be defined as placenta inserted in wholly or partially in the lower uterine segment. This also causes preterm labour.

Foetal causes

Birth defects were associated in preterm deliveries according to Dolan and colleagues (2007).

EPIDEMIOLOGY

RACE

Preterm birth rates vary with different ethnicities and races. According to Goldenberg and colleagues in 2008 Black, African-American and Afro-Caribbean have a higher risk of preterm birth. Recurrent preterm birth is seen in black women according to Kistka and Colleagues, 2007.

Gene in 1996 reported that the rate of pre-term birth in African American women (2000) was not influenced by social and demographic factors.

AGE:

Preterm birth is associated with parity and maternal age. Young multiparae and older primiparae have higher risks of preterm delivery. According to Lumley Jm et al 1993 the incidence of preterm delivery is high in mothers less than 17 and more than 35 yrs. Very young maternal age can contribute to preterm labour (Amini et al, 1996). According to Hediger et al, (1997) adolescent girls less than 16 years, have twice the risk of preterm labour considering with older women. At the other end, women aging 35 and over too higher preterm delivery risks (Astolfi and Zonna 2002)

WEIGHT

Poor nutrition, pre pregnancy weight and weight gain during pregnancy play an important role in causing preterm labour. Hickly and colleagues in 2005 have reported that low maternal weight gain is often associated with preterm birth.

STATURE

Short statured women have tendencies to deliver small babies. According to Lao and Ho, 1997 indicated that preterm delivery and labour risks was more in teenage pregnancies, and the occurrence was conversely related with maternal height. This proposed that the characteristic risk of preterm delivery in teenagers was short stature, which in turn could have been a reflection of young physical development during pregnancy.

SOCIOECONOMIC STATUS

The reasons for socioeconomic differences in preterm births are not clear, and have not been much explored. A number of reasons like maternal nutrition, smoking, abuse, activities, work and prenatal care have been implicated with preterm births. Women from lower socio

economic status tends to be less educated and would not have satisfactory general, prenatal and antenatal care (Goffinet F 2005)

Low socioeconomic status on health appears to directly affect the incidence of preterm labour (Moutquin, 2003). Many studies show an correlation between preterm birth and numerous socioeconomic issues like societal class, education, marital status, earnings. Maternal nutrition before and during pregnancy have contributed to the risk of preterm births, and this can be analysed by body mass index (WHO, 1995).

ADDICTIONS

Women who smoke and cocaine users are at increased risk of preterm labour (Bens 2004). The correlation between smoking and preterm birth was only existing among women with an increased intake of caffeine. Smoking more than 20 cigarettes per day has resulted in the increased incidence of pre-term birth under 34 week's gestation. Smoking initially associated with placental abruption, placenta praevia and pre mature rupture of membranes has now been linked with pre term delivery (Cnattingius 1998). Boer et al 1993, Volpe studied the increased incidence of pre-term birth in women addicted to opiods. Though, whether smoking alone effects the risk of preterm birth among heavy users of caffeine requires further investigation.

Studies show women who abuse cocaine have high incidence of preterm labour, and it was partly attributed to the abruption caused by cocaine addiction. (Boer et al)

Studies relating consumption of alcohol with the risk of pre-term labour are very few.

Occupational hazards

Those involved in manual work are more prone for preterm labour

PREDISPOSING FACTORS

Stress:

Preterm birth is associated with psychological factors such as depression, anxiety and chronic stress (Copper: 1996, Li 2008, Littleton 2007).Occupation which involve heavy physical work and psychological strain are associated with increased preterm births (Papiernik and Kaninski 1994).The utero placental flow decreases in prolonged standing and increases the frequency of placental infarcts causing intrauterine growth retardation. Preterm birth is increased in women who are subjected to physical abuse. Henribon et al 1995 reported that heavy vigorous exercise in the third trimester increased the risk of pre-term

delivery while regular and moderate exercise were actually showing a reduced risk.

Coitus

Various theoretical mechanisms have been proposed for initiation of labour by sexual activity. These are nipple and genital stimulus may induce oxytocin release from the posterior pituitary, initiating uterine contractions. Prostaglandins that is released from mechanical stimulation of the cervix may be the reason of cervical ripening and prostaglandins in semen may also cause cervical ripening. Mills and co-workers found in singleton low-risk pregnancies sexual activity did not increase the frequency of preterm labour.

The influence of sexual interaction on recurring preterm delivery in women with history of prior spontaneous preterm birth was studied by Yost and colleagues at less than 32 weeks' gestation and concluded that sexual intercourse had no effect on the occurrence of recurring preterm delivery. But the risk of recurrent preterm delivery increased with multiple sexual partners.

Reproductive History

a) Previous preterm birth

The risk of preterm delivery increases with a history of previous preterm delivery. Spong, 2007 concluded that previous preterm delivery was a major risk factor for preterm labour.

History of one previous preterm birth is associated with a recurrence risk of 16-41 % (Williams 22”’ edition).Preterm delivery risks increases with the number of preterm birth and decreases with term deliveries. This risk is on an increasing trend whenever the number of prior preterm births increases (Hoffinan 1981). Women having a prior preterm delivery have three times the risk of recurrence compared to a woman who has got a previous term delivery. This risk increases to eight fold whenever there is a history of two preterm deliveries. Though preterm delivery is an important risk factor to recurrent preterm delivery, previous preterm birth contributes to only 10% of total preterm births (Bloom and associates 2001). Factors such as cervical length and inherent biological property of the cervix may contribute to the recurrence of preterm births.

b) Previous abortion

Preterm deliveries increase in women who experienced one or more second trimester abortions. Earlier encouraged abortions were mainly linked with preterm delivery and the risk of preterm birth increased with the number of abortions. The extent of association with previous induced abortion varied according to the cause of preterm delivery. Prior encouraged abortions mainly increased preterm delivery risks after idiopathic preterm labour, preterm premature rupture of membranes and ante-partum haemorrhage, but not preterm delivery after maternal hypertension. The strength of the correlation increased with decreasing gestational age at birth.

c) Cervical incompetence

Cervical Incompetence is diagnosed clinically by recurrent painless cervical dilation and spontaneous mid trimester abortions in the absence of membrane rupture, bleeding or infection. . This can lead to protrusion of the membranes into the vagina followed by expulsion of the immature foetus. This may repeat in future pregnancies if not treated.

Some of the causes are previous traumatization of the cervix caused by

- Dilatation and curettage
- Conisation
- Cauterisation
- Amputation of cervix

According to Albrechten and colleagues (2008) there is a fourfold risk of pregnancy loss before 24weeks in patients who had undergone cervical conisation.

d) Uterine anomalies:

e) Pregnancy complications

- Multiple pregnanciesHydramnios
- Preeclampsia
- Antepartum hemorrhage
- Second trimester bleeding not due to placental causes

Interval between pregnancies

Interval between pregnancies play a major role in preterm labour. Intervals shorter than 18 months and longer than 59 months has

beenconsidered as increased risk for preterm & small for gestational age infants (Conde - Agudelo 2006)

Preterm births was increased if the interval between childbirth and LMP of next pregnancy was less than 3 months. Bloom et al in 2001 found athreefold increase in risk if previous birth was preterm compared to a previous term pregnancy. A previous occurrence of preterm birth before 34 weeks may increase the risk of recurrence. (Krymko et al 2004)

Foetal Gender

Male babies have an increased chance of preterm delivery compared to female babies.

PATHOGENESIS OF PRETERM LABOUR

The normal labour involves three components namely cervical ripening, myometial and foetal membrane activation. Preterm labour can be physiological or pathological if it occurs prematurely ordue to an abnormal stimulus respectively. Though etiology of preterm labour is multifactorial infection is implicated in initiation of preterm labour.

Withdrawal of progesterone theory established in parturition in sheep is not clear in humans. Increased synthesis of prostaglandins initiate parturition.

The intrauterine tissues synthesise prostanoids which play an important role in the commencement or maintenance of labour in a number of species. The amnion during labour produces more amount of PGE2 (Mitchell, 1986; Casey and MacDonald, 1986), which stimulates the physiological process leading to birth. Though the stimulus for preterm labour varies the final pathway involves the inflammatory mediators cytokines.

Cervical Ripening

This involves transformation of firm long cervix to soft distendable cervix. Cervix is predominantly made up of connective tissue namely fibroblasts and extracellular matrix. At end of pregnancy, there is increase

in collagenase activity and hyaluronic acid production which decrease the collagen content and increase the water content of cervix. Sex steroids and prostaglandins are involved in initiation of parturition.

Activation of foetal membranes

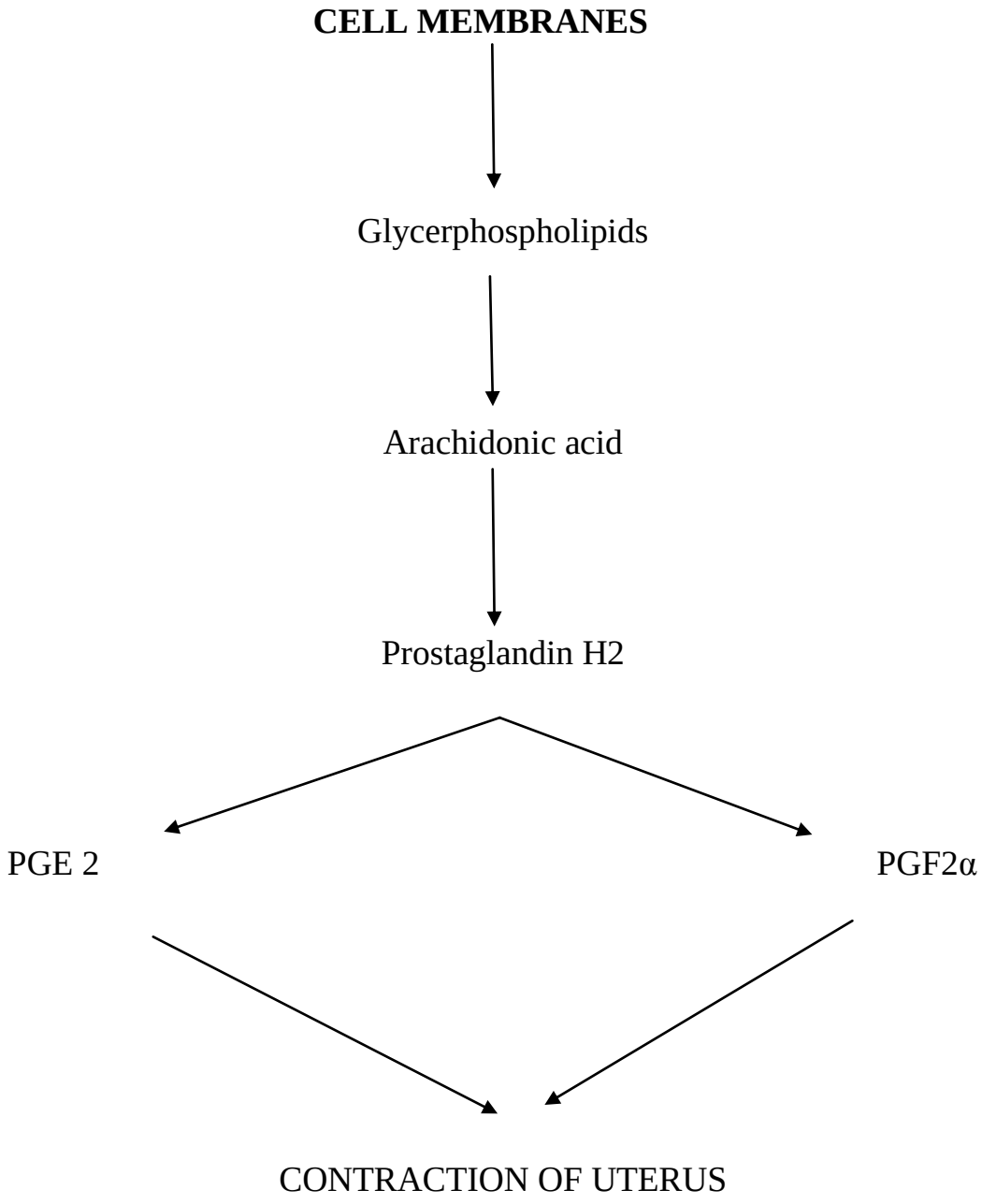
During pregnancy, the chorioamnionic membranes fuse with the decidua. Many biochemical reactions occur in term and preterm labour which cause the separation of the foetal membranes from the decidua which results in rupture of membranes. Fibronectins are present at the chorionic-decidual interface which are degraded and released into cervical and vaginal secretions immediately before term and preterm parturition. Beyond proteolytic degradation of the decidual and amniochorionic extracellular matrix by matrix-degrading enzymes, PROM is also associated with amnion epithelial apoptosis and localized inflammation. Enzymatic activity of matrix proteases are involved in the process of rupture of membranes and parturition with intact membranes.

Contraction of myometrium

In pregnancy uterine contractions are inhibited by progesterone, relaxin, and nitricoxide. At the end of pregnancy these substances reduce making the uterus respond to uterotonic agents. Increase in intracellular concentration of calcium is implicated in uterine contractions. Though

uterine contractions play a vital role in preterm labour compared to cervical ripening or foetal membrane activation studies involving myometrial activity are limited.

Prostaglandins play an important role in preterm labour. Csapo (1961) proposed that labour commenced when the balance between myometrial stimulants and relaxants is lost. Prostaglandin endoperoxide H synthase increases the rate first, committed step of prostaglandin synthesis from arachidonic acid (Smith et al, 1991). Prostaglandin endoperoxide H synthase activity increases in the amnion at parturition. According to DeWitt (1991) and Smith et al (1991), the prostaglandin endoperoxide H synthase expression is affected by various substances like growth factors, vascular cells, cytokines, steroids and tumour promoters in fibroblasts, and monocyte- and macrophage-like cells


CELL MEMBRANES
Glycerphospholipids
Arachidonic acid
Prostaglandin H2
PGE 2
PGF2α
CONTRACTION OF UTERUS

Role of Cytokines in Preterm labour

Cytokines such as interleukin 1, 2, 6 and 8 and tumour necrosis factor are implicated in preterm labour. Infection is associated with by a host-inflammatory response, which causes accumulation of inflammatory cells in the chorioamnionic membranes and thereby increasing the expression of cytokines .This inflammatory process can trigger the onset of preterm labour by myometrial contractions, PPROM and cervical ripening. This is supported by the fact that there is an increased cytokine levels (e.g. interleukin-6 [IL-6] and IL-8) in the amniotic fluid of patients with preterm labour. Interleukin 1 and tumour necrosis factor cause rupture of foetal membranes.

In Sweden a study conducted about the association between the intra-amniotic microbial colonisation and the levels of IL-6 and IL-8, and their association with preterm birth revealed that microorganisms in the amniotic fluid were detected in 16% of women in preterm birth and 25% of women with PPROM. It was also found that a high ratio of cases with preterm labour (43%) and PPROM (57%) hadraised IL-6 and or IL-8 levels in the amniotic fluid, indicating an inflammatory response.

Hence a solid relation between inflammation, microbialisation and preterm birth was established. Level of cytokines in amniotic fluid predicted preterm birth.

Interleukin-18 has also been found to play a major role in preterm labour. It is produced as a proform and is stimulated by the enzymecaspase-1. This in turn activates intracellular signalling pathway through interface with the IL-18 receptor causing pro-inflammatory molecules, like interferon-g, tumour necrosis factor-a (TNF-a) and IL-1.Hence IL-18 can be considered to play a vital role in infection leading to preterm birth. Levels of IL-18 seem to be raised in the cervical and amniotic fluid of women in preterm labour compared with those not in labour at term.

DIAGNOSIS OF PRETERM LABOUR

Cunningham Gil and co-workers (2001) found that preterm labour is established when regular uterine contractions occur at least 4 in 20 minutes or 8 in 60 minutes with progressive change in cervical score with effacement 80% or more and dilatation more than 1 cm occurs. Preterm labour can be diagnosed by various factors .Preterm labour can be diagnosed by clinical methods and by investigations.

Threatened preterm labour is a condition in which uterine contractions occur in the absence of cervical changes.

PAPIERNIK SCORING SYSTEM

Points	Socioeconomic factors	Previous Obstetric /Medical History	Social	Aspects of current Pregnancy
1	Two living children low socioeconomic status	H/o 1 abortion / less than 1 year of last child birth	Employed	Unusual fatigue
2	Maternal age <20 or >40 years/single parent	H/o 2 abortions	Smoker 10 Cigarettes/ day/ moderate work	Gain <5g by 32 weeks
3	Very low socioeconomic status Ht< 150cm wt<45 kg	H/o 3 abortion	Heavy work / long distance traveling	Breech 32 weeks/ weight loss /head engaged at 32 weeks / febrile illness
4	Maternal age <18 year	Pyelonephritis		Bleeding after 12 weeks / short cervix open internal OS uterine irritability
5		Uterine anomaly second trimester abortion /DES exposure/cone biopsy		Placenta Praevia Hydramnios
6		Preterm delivery ,repeated second trimester abortion		Twins/ abdominal surgical procedure

SYMPTOMS

- Menstrual like cramps
- Low dull back ache
- Increase or change in vaginal discharge
- Uterine contractions 10 minutes apart or closer

CLINICAL ASSESSMENT

Uterine contractions

Uterine contractions is the main symptom of preterm labour. There should be regular uterine contractions of at least 4 in 20 minutes or 8 in 60 minute each lasting not less than 40 seconds.

Uterine Activity Monitoring

Although teaching a woman to self-monitor her uterine contractions is a simple inexpensive method, there are lot of subjective variations in it which makes it less reliable .The perception of the contractions in terms of frequency ,intensity, duration may vary between the health care providers hence a tocodynamometer can be used to assess the contractions. One of an earlier case control study reported a decrease

in the preterm delivery rates on using the ambulatory monitoring system. (Katz et al 1986).

Current opinion is that for most patients home uterine monitoring is no better than frequent nursing care and support. Only patients, who cannot recognize the presence of uterine contractions adequately like multi foetal gestation and over distended uterus may benefit from home monitoring.

These contractions are accompanied by progressive cervical changes.

CERVICAL ASSESSMENT

The clinical diagnosis of labour is dependent on the presence of uterine activity with cervical effacement and dilation. One of the main sign of term or preterm labour is cervical change. When patients come with the complaint of pain after confirming uterine contractions pelvic examination is done. The following features are assessed namely position, consistency, dilatation, effacement of the cervix. This digital examination is not precise as there are inter- and intra-operator errors.

CERVICAL LENGTH

Cervical length measurement by digital examination formed the gold standard for diagnosis of preterm labour. Women with shorter cervices experienced increased rates of preterm birth.

The manual assessment of cervical length is subjective and has poor inter and intra observer variability. The cervix shortens and dilates at the level of internal cervical os. This process cannot be appreciated on a digital examination. Transvaginalultrasound examination of cervical length is better than digital examination in predicting preterm delivery. Hence cervical length measurement by ultrasound is used for prediction of labour.

The normal way of evaluating cervical length is by endo-vaginal ultrasound. Different measurements have been used to define short cervix. In patients with short cervical length, the “T” that is seen in ultrasound of cervix becomes “Y” and later on “U” as the amniotic sac descends. Though the conclusion of a short cervix does not mean incompetence and it is only a proposal, and neither can it identify, the pathological reasons for it. Before 1994, the studies done were surveyed by cerclage, making it harder to confirm. Later Jams et al; 1994, reported

a means cervical length at 24 weeks around 35mm with progressively shorter cervix had more changes of preterm delivery.

Owen and co-workers concluded in 2003 that the value of cervical length to predict birth before 35 weeks is apparent only in high risk patients for preterm delivery .Studies by De Caralto et al 2005correlated the cervical length to preterm delivery. Hassan et al 2000 & 2001, found that when the cervical length was less than 25 mm, there was a high chance of preterm delivery with the normal mean length of cervix at 23 weeks of gestation being 35mm to 38 mm with the 10^{th} and 90^{th} percentile being 25mm and 45mm respectively.

A cervical length of 21mm at less than 20 weeks of gestation was shown by Cook et al (2000) to be associated with high risk preterm delivery. Owen et al (2001) showed at 3.3 time's higher risk for preterm delivery if the cervical length of 25 mm or less is seen at 16-19 weeks of pregnancy. An ultrasound screening every two weeks was also found to be significantly helpful (Andoers et al 2000).

FUNNELING

In women who are prone to deliver prematurely herniation of the foetal membranes occurs into the upper part of the endocervical canal.

Although the length, width and relationship of funnel to cervical length have been studied, there are no uniform criteria to describe funnelling. The reporting of funnelling as present or absent on ultrasound is a significant conclusion to be cited as its found equivalent to dynamic cervical changes. Rust et al (2005) showed the risk of preterm labour, higher incidence of complication and cerclage placement in women with both cervical shortening and funnelling.

Dynamic cervical changes

The opening of the internal os and descent of the foetal membranes on fundal pressure during ultrasound was found to be significant risk factor for preterm labour (Gwzman et al, 1994). Passive or dynamic ultrasound finding of shortening of the cervix between 15 and 22 weeks is a significant predictor of additional cervical shortening (Gwzman et al, 1997). The myometrial activity in painless uterine contractions leads to dynamic changes and is an indication that that the cervix is opening during these contractions.

Cervical dilatation

A study by Papiemik and his colleagues (1987) on cervical status before 37 weeks, concluded that risk of preterm labour is increased by precocious cervical dilatation. According to Levino and associates, one in

four women who had dilated cervices (2-3cm) between 26 and 30 weeks, had their delivery before 34 weeks. Copper and associates (1995) have found that asymptomatic cervical dilation that occurs after mid pregnancy is significant preterm labour risk reason. Pereira and co-workers, (2007) identified cervical dilation as a predictor of a higher preterm delivery risk.

CERVICAL INCOMPETENCE

Premature cervical dilatation is associated with increased risk of preterm labour (Papiemik and colleagues 1987).In a study by Levino and associates one fourth of the women who cervices were dilated 2 to 3 cm between 26 and 30 weeks delivered before 34 weeks .Asymptomatic dilatation of cervix after mid trimester is considered as a risk factor for preterm labour. In a study by Cook and Ellwood. Cervical status of nulliparous and parous women between 18 and 30 weeks was followed up and both the groups gave birth to term. Copper and associates in 1995, Pereira and colleagues in 2007 have suggested cervical dilatation as an increased risk for preterm labour.

INVESTIGATIONS

Foetal fibronectin

Foetal fibronectin is produced in 20 different types of molecular forms by different kinds of cells. These includes hepatocycles, fibroblasts, endothelial cells and foetal amnion. Foetal fibronectin is found in high concentration in both maternal blood and amniotic fluid. They are thought to play an initial role in intercellular adhesion during implantation and in maintaining placental attachment to the exterior decidue according to Lesson and colleagues (1996).

Foetal fibronectin is found in cervical secretions in term patients and normal patients with intact membranes. This denotes stromal remodelling of the cervix before labour. It is normally found in cervico vaginal secretions before 16-18 weeks gestation before the fusion of the foetal membrane to the decidual and then towards term prior to the onset of labour. It is usually not found between 22 and 37 weeks of gestation.

Lockwood and co-workers in 1991 reported that fibronectin in cervicovaginal secretions can be considered as a marker for impending preterm labour. Swabs taken from posterior fornix or cervix is used for the detection of foetal fibronectin by ELISA method with FDG 6 monoclonal antibody. Value exceeding 50 mg/ml is considered as

positive. Quantitative tests takes a longer time to develop, hence bedside tests have been developed. High false positive rates are there if sample is contaminated with amniotic fluid, semen, maternal blood, patients with encirclage. Goldberg and co- workers in 2000 reported detection of fibronectin in the vaginal or cervical secretions as an important predictor of preterm labour.

Leitich and co-workers performed a comprehensive meta-analysis on the efficacy of foetal fibronectin in identifying women at risk for preterm delivery. They noted that the test's usefulness was a result of its high specificity and was limited by the low sensitivity in identifying women who would go on to deliver prior to 34 weeks gestation. The sensitivity of the test decreased further in identifying women who would deliver prior to 37 weeks but increased when it was used serially.

In order to maximize foetal fibronectin, its use should be restricted to women with intact membranes, cervical dilation less than 3 cm, and gestational age between 24 and 34 completed week’s gestation, and results should be available within 24 hours. False-positive foetal fibronectins may be obtained in women with recent intercourse or vaginal examinations or in the presence of bacterial vaginosis and vaginal bleeding.

In general, the sensitivity of foetal fibronectin increases in symptomatic women, women with a cervical length of less than 2.5 mm, women with a history of prior preterm delivery, and women with bacterial vaginosis. The negative predictive value in women with preterm contractions ranges from 69% to 92% before 37 weeks gestation. Importantly, a negative foetal fibronectin has a 95% likelihood that delivery will not occur within 14 days of sampling.

The Preterm Prediction Study of the National Institute of Child Health and Human Development analysed the sensitivity, specificity and predictive values of Bishop Score, fibronectin test and cervical length in predicting preterm labour in asymptomatic women (Iams et al, 2001)

CERVICAL PHOSPHORYLATED INSULIN LIKE GROWTH FACTOR BINDING PROTEIN -1

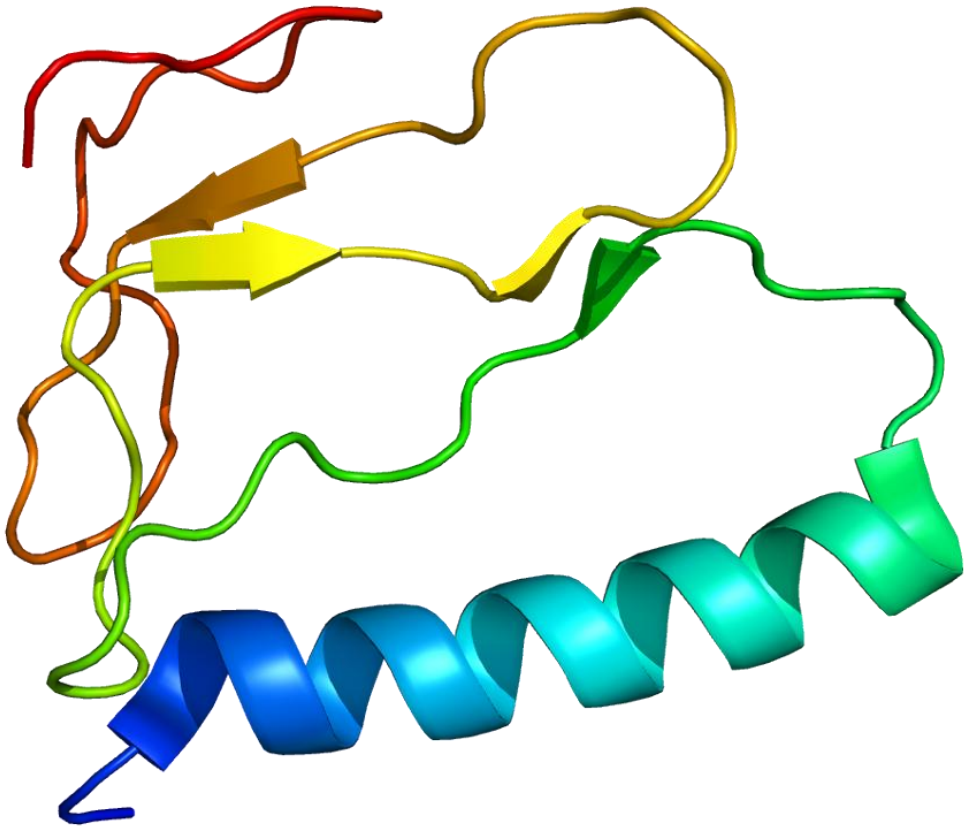
Diagnosis of preterm labour poses a major problem. Any test that can precisely diagnose preterm labour will be of much help. One of the latest modality in predicting preterm labour is phosphorylated insulin like growth factor binding protein -1 in cervical secretions.

Insulin-like growth factor-binding protein 1 also known as placental protein 12 is a protein that in humans is encoded by the IGFBP1 gene . The gene encoding for insulin like growth factor binding protein 1 is localised on human chromosomal region 7 p14-p12.

Insulin like growth hormone is a single chain polypeptide 70 amino acid residue, cross linked by three Disulphate Bridge. The Molecular weight is 7649.It is homologous to proinsulin; 1 to 29 are homologous to insulin B and 42-62 to insulin chain A. An octopeptide sequence at COOH terminal end is not found in proinsulin.

Insulin like growth factor binding protein-1 belongs to a super family of insulin like binding protein. Insulin like growth factor of both type’s l and ll are involved in the control mechanism of foetal placental

growth and development. Binding of this protein prolongs the half-life of the IGFs and alters their interaction with cell surface receptors. Insulin like growth factor binding protein 1 is secreted from the adult and foetal liver. The maternal concentration of insulin like growth factor binding protein 1 increases as pregnancy advances and forms a major constituent of amniotic fluid from second trimester onwards. Its concentration in amniotic fluid is 100-1000 times higher than that found in the plasma.



Insulin Growth Factor Binding Protein

There are six subtypes insulin like growth factor binding protein-1 and the highly phosphorylated isoform is found in decidual tissues secreted the decidual cells. The non- phosphorylated and the lesser phosphorylated is form is found in amniotic fluid. The difference in the origin of insulin like growth factor can be detected with the use of monoclonal antibodies. During the process of labour, the choriodecidual interface is disrupted releasing the phosphorylated insulin like growth factor binding protein -1 into the cervical secretions. Bed side kits have been developed for the qualitative detection of phosphorylated insulin like growth factor binding protein -1 above 10mg/l.

AMNIOCENTESIS TO DETECT INFECTION:

There are several tests to analyse intra-amniotic infections. Tests done by Romero and his colleagues in 1993 in 120 women with intact membranes and preterm labour, were used to assess the value of amniotic fluid that had increased leukocyte counts, elevated interleukin -6 concentration or a positive Gram stain, and reduced glucose level.

Those results with positive amniotic fluid culture were counted as infected. The experiments concluded that a negative Gram stain result was 99% to dismiss amniotic fluid bacteria. An increased value of

interleukin-6 level, was 82% sensitive for finding out amniotic fluids that has bacteria.

There are other studies by Andrews and co-workers (1995) and Yoon and colleagues (1996) which have also proven that there exists a relation between the amniotic fluid inter leukin-6 levels (or leukocyte levels) and chorioamnio infections. Although these studies prove the relationship between the two, it is not confirmed that amniocentesis to identify infection is related with improved pregnancy results with or without rupture of membranes in women (Einstein and co-workers, 1986).It is determined that there is no indication to support routine amniocentesis to detect infection.

OTHER BIOCHEMICAL MARKERS

1. Salivary oestriol> 1.8/mi before 34 weeks has sensitivity of 68% and specificity of 76% for preterm labour before 35 weeks of gestation(Darne et al)
2. Serum collagenase
3. Tissue inhibitor of metalloproteinase (TIMP)/Matrix metailoproteinases
4. Relaxin
5. Corticotrophin Releasing Hormone
6. Human chorioniegonadotrophin

These are of less practical value in prediction of preterm labour

Mediators of Inflammation and Infection

a. C — Reactive protein

b. Granulocyte elastase

c. Cytokines (IL-6, TNF)

d. Amniotic Fluid Glucose Concentration

e.Zinc

f. Lipocortin -l (Romeo R et al)

g. Positive cultures

h. Granulocyte colony stimulating factor

These are not practically helpful in prediction of pre-term labour.

MANAGEMENT OF PRETERM LABOUR

The management of preterm labour includes

- To prevent preterm onset of labor if possible
- To arrest labor if not contraindicated
- Appropriate management of labor
- Neonatal care

PREVENTION OF PRE TERM LABOUR

Prevention is an important strategy in the management of a patient at high risk of preterm labour. The following guidelines are adopted:

i) Primary care

Aimed to reduce incidence by reducing the high risk factors.

ii) Secondary care

Screening for early detection and prophylactic treatment.

iii) Tertiary care

Aimed to reduce the perinatal morbidity and mortality after the diagnosis.

Basic care

Development of family support, education, supportive services from health care providers

- ❖ Behavioural and life style modifications
- ❖ Adequate nutrition.
- ❖ Cessation of smoking (Burguet et al)
- ❖ Avoidance of illicit drugs

Bed rest, hydration and sedation

Although bed rest and hydration are widely used as the first step of prevention, its practical benefit has been debatable. (Golden berg RL et al)

Kovacevich et al in his studies showed that bed rest of more than three days was associated with an increased occurrence of thrombocmbolic events in women with threatened pre-term labour.

Some studies have reported the increased risk of development of pulmonary edema, when intravenous fluids are administered during tocolytic therapy. There is no substantial evidence of hydration therapy in causing pregnancy prolongation. Hydration therapy however has been

rarely studied as a single therapy in prevention or treatment of pre-term labour.

Cochrane systematic review showed no significant difference in the risk of pre-term labour in women who received hydration therapy. Comparative trials have been conducted between combination of sedation with hydration vs intramuscular opiods in reducing the occurrence of preterm delivery and the results were found to be similar in both groups.

Treatment of infections

About 25 — 40 percent of preterm births are estimated to result from intrauterine infections (Cunningham et al 2010) Morency and Buyold (2007) seemed to indicate that antibiotics given in the second trimester to females with a past of preterm labour would be effective in preventing reappearance of preterm labour

Most Randomized control trials show that intra vaginal clindamycin cream used to treat bacterial vaginosis did not reduce the rate of preterm birth. Carey et al (2000) used oral metronidazole to treat bacterial vaginosis but did not find a reduction in preterm birth. Methodical evaluation determined that screening and treatment of asymptomatic bacteruria and bacterial vaginosis may lessen the occurrence of preterm in low risk population

Cervical encirclage

Primary circlages are placed prophylactically in women considered at high risk of preterm birth based on obstetric history. Secondary circlages are placed when ultrasound findings are indicative of cervical insufficiency in high risk women.

Tertiary circlages are done as an emergency process in the presence of positive clinical examination findings. The 1993 MRC/RCOG Multicenter Randomized experiment determined that clear benefit was seen only in patients with a history of three or more spontaneous births or preterm deliveries (Mac Naughton et al 1993)

In 2001, CIPRACT Trial, Cervical Incompetence Prevention Randomised Cerclage Trial showed that patients with cervical insufficiency and cerclage placement had a lower incidence of preterm delivery prior to 34 weeks (ALTHUISIUS ET AL 2001)

Rest Ct al 2000 concluded that cerclage failed to alter any perinatal outcome Daskalakis et al (2006) reported the benefits of emergency cerclage. In preterm labour Dor et al 1982 and Roman et al 2005 reported that elective cerclage had no benefit in twin gestation. Two randomized trials by Lazr et al and Rush et al showed no benefit of routine cerclage in women at moderate risk for preterm labour.

EMERGENCY OR RESCUE CERCLAGE

There are certain studies that show that cervical incompetence and preterm labour together may lead to preterm delivery. Studies have analysed the importance of cerclage that is done after preterm labour initiates. If cervical incompetence is found with risk of preterm labour, emergency cerclage can be tried, although there is risks of pregnancy loss and infection (Harger, 1983). In an experiment conducted by Althuisius and his co-workers, among 23 women with cervical incompetence before 27 weeks patients were subjected to bed rest with or without McDonald cerclage. The result was, that delivery delay was more in the group with cerclage than that of bed rest alone by 54 and 24 days respectively.

Another study was done by Terkildsen and his colleagues in 2003 that included 116 women for whom second trimester emergency cerclage was attempted. Membranes that extended outside the external cervical os and cerclage before 22 weeks, were linked with substantial decreased occurrence of pregnancy continuance to 28 weeks or more.

Progesterone

Progesterone given as weekly intramuscular injections of 17 hydroxyl progesterone caproate from 16-20 weeks to 37 weeks showed significant decrease in preterm labour (Meis et al 2003) .It is not beneficial in twin pregnancies (Rouse et al 2007) (.Fonseca et al 2007) Micronized progesterone for asymptomatic women with very short cervix (Less than 15mm) appear to be effective for prevention of preterm delivery.

As per AGOG (2008) progesterone is not recommended as a supplementary treatment to cervical cerclage for suspected cervical insufficiency or .as a preventive agent for asymptomatic women with a positive foetal fibronectin screen result or as a tocolytic agent. The role of progesterone in threatened preterm labour is uncertain (Cochrane Systematic Review 2006).

Cortico steroids

The potential for antenatal administered corticosteroids to accelerate lung maturity was discovered by Liggens. In 1995 National Institute of Health consensus Development Panel recommended corticosteroids for foetal lung maturation in preterm infants, antenatal

corticosteroids are recommended for all pregnant women between 25 and 34 weeks who are at risk of preterm delivery within 7 days.

The initial reason for the usage of steroids in women with preterm delivery risk, was to avoid neonatal respiratory distress syndrome. After analysing a number of steroids administered pregnant women, it was revealed that there was another important benefit, which was the prevention of neonatal IVH. As there are such significant benefits of steroids administration, that overcome most of the theories that object such an approach about steroid usage, strong reasons must be justified for not using this treatment, especially in cases when preterm labour is going to occur before 30 weeks.

Cochrane systematic analysis reported that antenatal corticosteroids reduce neonatal death respiratory distress syndrome, intra ventricular haemorrhage, necrotizing enter colitis in first 48 hours of life as well as reduction in the need for intensive care monitoring & respiratory support later

For women with established preterm labour, a mix of betamethasone acetate (6mg) and betamethasone phosphate (6mg) must be administered intramuscularly, in consecutive two doses, with 24 hours

interval, with no contraindications for steroids. Some even prefer to use dexamethasone 4mg IM, for four doses every six hours.

Roberts and Daiziel (2006) reviewed antenatal corticosteroids for accelerating foetal lung maturity Bruschettini and colleagues (2006) studied equivalent of 12 mg versus 6 mg beta methadone and reported that the lower dose had less severe effects on somatic growth without affecting cell proliferation Eli main and co-workers (2007) reported that beta methasone and dexamethasone were comparable in reducing the rates of major neonatal mortalities in preterm infants.

According to Crowley, 1995, proposes that the effect of glucocorticoids, on foetal lung lasts not more than one week, through meta-analysis of random clinical trials. After this finding, the practice of administration of booster dose of betamethasone for every week for those who remained undelivered seven or more days after the early treatment, was adopted by many obstetricians.

Nevertheless, there are evidences that such a practice is linked with major fetal and neonatal side-effects, and it should be abandoned (Debbs et al, 1997; Banks et al, 1999; Vermillion et al 1999, Jobe et al, 1998; French et al, 1999)

Though the maximum benefit of corticosteroid administration is between 24 hours and 7 days after initiation of therapy they provide surgical advantage even when baby is delivered within 24 hours.

RESCUE

Rescue means giving a repetitive dose of corticosteroid when delivery is about to happen and more than 7 days have passed from the time of the first dose. It is said that rescue therapy should not be repetitively used and must be used mostly for clinical trials according to 2000 Consensus Development Conference.

In the trials conducted by Peltoniemi and his co-workers in 2007, that allotted 326 women to placebo or 12 mg betamethasone single dose rescue treatment. It concluded that the rescue dose increased the risk of respiratory distress syndrome. Later the American College of Obstetrics and Gynaecologists (2008) too recommends such method for trials.

Recently in a study of 437 women, less than 33 weeks who were administered rescue therapy or placebo, found that it reduced the rates of respiratory complications, and neonatal composite morbidity, with rescue corticosteroids according to Kurtzman and co-workers, 2009. However there were nil differences in perinatal mortalities and other morbidities. There are also evidences that treated infants had better respiratory compliance (Mc Evoy and associates, 2009).

PRINCIPLES OF MANAGEMENT IN WOMEN WITH PRETERM LABOUR

1. Steroids to the mother to enhance lung maturity.
2. Antenatal transfer of the mother to a center equipped with NICU
3. Tocolytic drugs
4. Antibiotics
5. Careful intrapartum monitoring
6. Vaginal delivery preferred unless cesarean birth is indicated.

RECOMMENDED MANAGEMENT OF PRETERM LABOUR

AGE: 34 weeks or more

MANAGEMENT:

- Proceed to delivery, usually be initiation of labour
- Group B streptococcal prophylaxis is suggested

AGE: 32 weeks to 33 completed weeks

MANAGEMENT:

- Expectant management unless fetal pulmonary maturity is documented
- Group B streptococcal prophylaxis is recommended

- Corticosteroids-no consensus, but some experts recommend.
- Antimicrobials to prolong latency if no contracindications.

AGE: 24 weeks to 31 completed weeks

MANAGEMENT

- Expectant management
- Group B streptococcal prophylaxis is recommended
- Single course corticosteroids use is recommended.
- Tocolytics – no census
- Antimicrobials to prolong latency if no contraindications.

AGE: Before 24 weeks

MANAGEMENT:

- Patient counselling
- Expectant management or induction of labor
- Group B streptococcal prophylaxis is not recommended
- Corticosteroids use is not recommended.
- Antimicrobials-There are incomplete data on use in prolonging labor.

TOCOLYTIC AGENTS

Tocolysis is pharmacological suppression of uterine activity.

Tocolytic drugs have been used in an attempt to inhibit preterm labour. They are effective in reducing the likelihood of delivery within 48 hours but do not reduce the overall risk of preterm labour. (ACOG 2007)

Tocolytics may be required

1. To gain 48 hours to administer antenatal steroids for increasing pulmonary maturity
2. To permit in utero transfer of the patient to a tertiary care centre for Multi disciplinary management
3. Prepare for neonatal care
4. Preparing the patient for an operative delivery

Variety of drugs which act on uterine smooth muscle to interrupt contractions are available these include magnesium sulphate, calcium channel blockers, oxytocin antagonists, Non-steroidalanti-inflammatory drugs (NSAIDS) and beta mimetic agonists.

As per ACOG 2003, choice of tocolytic agent is individualized and is usually based on the maternal condition.

Absolute Contraindications to tocolytic therapy

- Severe preeclampsia
- Severe abruption
- Severe bleeding, any cause
- Frank chorioamnionitis
- Foetal death
- Foetal anomaly incompatible with life
- Severe foetal growth restriction
- Mature lung studies
- Maternal cardiac arrhythmias

Relative Contraindications to Tocolytic Therapy

- Mild chronic hypertension
- Mild abruption
- Stable previa
- Maternal cardiac disease
- Hyperthyroidism
- Uncontrolled diabetes mellitus
- Foetal distress

- Foetal anomaly
- Mild intrauterine growth restriction
- Cervix greater than 4 cm dilated

β SYMPATHOMIMETICS

Cartis et al noted that small dose of epinephrine inhibited uterine hyperactivity .Efforts to produce an epinephrine like compound which lacked the cardiovascular stimulant effect culminated in the synthesis of beta agonists.

They react with β adrenergic receptors to reduce intracellular ionized calcium levels and prevent activation of myometrial contractile proteins Beta mimetics can cause mild fall in diastolic blood pressure and isused cautiously in patients of ante partum haemorrhage. They also cause a slight increase of blood sugar in non-diabetic patient and hence can cause gestational diabetes when used for a longer duration alter thyroid function, elevated transaminases hypo calcemia, anti-diuresis and hypo kalemia are the other metabolic effects of beta mimetics.

Some of the neonatal side effects of beta mimetics include increased risk of hypo calcemia, hypo glycaemia and interventricular haemorrhage. In recent time better drugs have replaced beta mimetics in regard to tocolytic function due to better profile of safety and less of adverse effects.

CLASSIFICATION

1st Generation: Isoxsuprine, Orciprenaline, Isoprenaline

2nd Generation: Ritodrine, Terbutaline, Fenoterol

The most common used beta 2 agonist for tocolysis is ritodrine; then is terbutaline and salbutamol.

RITODRINE

Merkatz and colleages 1980 achieved a gestational age of 36 weeks in patients treated with ritodrine for threatened preterm labour.It is given as infusion at a dose of 50 ig/min and increased every 20 minutes until uterus is quiescent or side effects limit escalation of dose.

- However the drugs have been implicated as a cause of increased capillary permeability, disturbance of cardiac rhythm and myocardial ischemia.
- Side effects are palpitations, tremor, nausea, headache, chest pain dyspnea, pulmonary edema, hypokatemia, myocardial ischemia and arrhythmias.
- Ritodrine was withdrawn voluntarily in 2003, according to Federal Register, United States owing to its adverse effects.

TERBUTALINE

Not used as much as ritodrine, but is effective in temporary suppression of uterine contractions when given parenterally.

- intravenous dose 5-10 1g/min ,increased every 10-15 mm to a maximum of 80 g. 2.5 — 5 mg is the oral dose given every 4-6 hours and 250pg subcutaneously every 20-30 minutes given as 4-6 doses.

- Terbutaline causes more hyperglycaemia than ritodrine

Like ritodrine it can cause pulmonary edema (Angel and associates 1988)

Gunin and associates (1998) reported no significant prolongation or improved neonatal outcome with terbutaline is not approved by the FDA and therefore it's not mentioned in any protocol for pre-term labour. Beta 2 agonists are no longer the first choice of drugs because of their side effects (RCOG 2002, Anotayanoth et al 2004)

Contraindications of beta 2 agonist :symptomatic cardiac disease, conduction disturbance, hyperthyroidism, sickle cell disease, uncontrolled diabetes mellitus, chorioamnionitis, severe preeclarnpsia, multifetal gestation and severe obstetrical bleeding.

Prostaglandin Inhibitors

Acetylsalicylate (Aspirin), Indomethacin naproxen fenamate, sulindac inhibit prostaglandin syntheses enzyme responsible for the transformation of free arachidonic acid to prostaglandins thereby decrease the myometrial gap junctions and influx of calcium.

Indomethacin was first used as a tocolytic by Zuckerman and colleagues (1974) various trials compared indomethacin with other drugs like ritodrine; Magnesium sulfate and found no difference in efficacy (Morales and coworkers (1989, 1193a).

Indomethacin is administered orally or rectally. A dose of 50 to 100 mg at 5 hours intervals, not to exceed 200 mg in 24 hours period.

Adverse effects reported are oligohydramnios, pulmonary hypertension due to constriction of ductus arteriosus. Intra cellular haemorrhage, necrotizing enterocolitis have also been reported.

Two randomized trials which compared the effect of indomethacin and placebo in delaying delivery showed no significant delay at 48 hours and 7 - 10 days.

Magnesium sulphate

Ionic magnesium in a sufficiently high concentration can alter myometrial contractility. Its role is presumably that of a calcium antagonist causing less intracellular calcium (Ca2+) to participate in actins myosin interaction during smooth muscle contraction. Elliott in his study found that Magnesium sulphate was effective tocolytic in 87% cases.

Cox and associates in their study did not report any differences in the pregnancy outcome using magnesium sulphate. It affects neural transmission by modifying acetyl chloline release and sensitivity of motor end plate.

Drug concentration and effect

- Contractility is inhibited at serum level of 5 - 8 mEq/L.
- Deep tension reflexes are lost at 9 - 13 mEq/L.
- Respiratory depression occurs at> 14 Meq/ dl

Loading dose of 4g IV given over 20 minutes followed by maintenance dose of 1-2 g / hour.

Side effect is nausea, giddiness, flushing, hypocalcemia, respiratory depression, pulmonary edema and depressed motor respiratory

activity in fetus. Contraindications of magnesium sulfate are myasthenia gravis, heart block, renal disease and recent myocardial infarction.

Neuro protective effect of magnesium sulfate was evaluated in (BEAM study-Beneficial Effects of Antenatal Magnesium Sulfate) According to Gowther et al 2002, Cochrane systematic review, magnesium sulfate is an ineffective tocolytic. Wilkens et al 1989 reported the occurrence of significant side effect of magnesium sulphate while being used concurrently with beta mimetics for tocolysis.

CALCIUM CHANNEL BLOCKERS

These agents act by reducing the influx of calcium ions into the cell membrane during the inward calcium current of action potential. They block the voltage sensitive L type of calcium channels. They also decrease the tone of smooth muscles by inhibition of intracellular calcium from sarcoplasmic reticulum .Nifedipine is the most commonly used calcium channel blocker.

King and colleagues 2003, Papatson's 1997 concluded that calcium channel blockers especially Nifedipine are safer and more effective tocolytic agents than are beta agonists and have lower neonatal morbidity No significant change in utero placental flow has been reported .Mari et al (1989)

TREATMENT REGIMEN

Optimal dose regimen of Nifedipine has not yet been defined. George et al 1991, Read and WeIlby (1986), showed that initial dose of 30 mg followed by 20 mg 8th hourly for 3 days had a success rate of 75% Andrenne et al gave a dosing regimen of 30 mg oral followed by a maintenance dose of 10 - 20mg orally every 4 - 6 hours.

Most trials advocated an initial loading dose of 30 mg of oral Nifedipine followed by 10 to 20 mg every 6 hours. Sublingual Nifedipine is no longer advocated due to risk of sudden hypotension. Onset of action is less than 20 minutes with peak plasma concentration within 15 - 90 minutes.

Having a half-life of 1.5 to 3 days. Elimination is mainly through kidneys (70%) and bowel 30%. Though the duration of action of a single dose can be as long as 6 hours, there is no apparent cumulative effect when administered every 6 hours.

Side effects include facial flushing, nausea vomiting, headache, hypotension and tachycardia. No significant alteration in blood glucose and serum electrolytes was reported.

OXYTOCIN ANTAGONIST (ATOSIBAN)

Nona peptide oxytocin analogy is a competitive antagonist of oxytocin induced contractions.

Dosage

Recommended dose and administration schedule is a three step procedure. The initial bolus dose is 6.75 mg given over one minute, followed by an infusion of 18 mg/hour for three hours and 6 mg/hour for up to 45 hours. Treatment should not last longer than 48 hours and total dose given should not exceed 330 mg (RCOG, clinical Guidelines 2002)

Side effects include nausea, vomiting, chest pain, and dyspnoea.

In randomized clinical trials, artesian failed to improve relevant neonatal outcome and was linked with significant neonatal morbidity (Moutquin and co-workers, 2000 Romero and associates 2000)

However, RCOG clinical guidelines 2002 suggested the first choice on administration of tocolytic to be oxytocin antagonist or Nifedipine.

NITRIC OXIDE DONORS (GLYCERYL TRINTRATE)

It is a potent endogenous hormone having smooth muscle relaxant property. Main action affects vasculature, gut and uterus. Nitric oxide donors act by inhibiting CRH (Corticotrophin releasing hormone), a promoter of parturition.

Dosage 10 mg Glycerol Tri nitrate patch placed over fundal region of maternal abdomen. Dose can be repeated with another 10 mg after one hour, if tocolysis is not achieved, to a maximum dose of 20 mg in 24 hours. Maternal hypotension is a common side effect.

In randomized clinical trials, Nitro glycerin administered orally, transdermal or intravenously was not effective and was no superior to other tocolytics (Bistis 2004, Clavin 1996, Rees 1999, Buhimschi 2002. DuckittK et al (2002) reported that nitroglycerine did not improve neonatal outcome or delay delivery on comparison with placebo, no treatment or alternative tocolytics.

POTASSIUM CHANNEL OPENERS

Diazoxide is related to thiazide diuretics and its main use is in the treatment of malignant hypertension. Its mechanism of action is inhibition of smooth muscle contractility, thereby causing uterine quiescence.

It is given in a dose of 5mg / kg, slow intravenous over 20-30 minutes. The drug is given after diluting with saline. Bolus dosage includes 50 -100 mg given every 5 minutes.

Side effects are tachycardia, hyperglycaemia, decreased blood pressure, and decreased utero placental flow secondary to hypotension in the mother. Hypoglycaemia and foetal distress are the side effects which occur secondary to maternal hypotension.

FETAL AND NEONATAL RISKS

Compromised foetal health is often the precipitating factor in threatened or actual preterm labour. Hence, intrauterine foetal death, intrauterine growth restriction, major congenital anomalies, unrecognized intrauterine infection, and complicated multiple pregnancy will all contribute to the perinatal mortality and morbidity rates associated with preterm labour.

RISKS OF PREMATURITY

The gestational age at which threatened or actual preterm labour presents, together with the birth weight, influences both the management and the outcome. In women presenting between 20 and 24 weeks' gestation, the management decision after discussion with the parents may be to allow delivery to occur because of the maternal risks from treatment

and the likely poor prognosis for the baby if, delivery can be postponed only for a few hours or days.

Foetal intrapartum hypoxia and birth trauma associated with preterm labour involving the very low birth weight infant, whether birth is by the vaginal or abdominal route, will contribute to the perinatal risk. The risks in the neonatal period are those of congenital malformation, intrauterine growth restriction, respiratory distress syndrome, necrotizing enterocolitis, intracranial haemorrhage, convulsions, and septicemia. The foetal and neonatal risks associated with the medical management of preterm labour have not been accurately quantified, but they require consideration in the overall management.

FETAL RISKS OF TOCOLYTIC AGENTS

Beta-sympathomimetic tocolytic agents cross the placenta and may cause foetal tachycardia and occasionally other adverse foetal cardiac effects, which may be significant in an already compromised foetus. The maternal hyperglycaemia commonly associated with the use of these agents may result in neonatal hypoglycaemia. There is a suggestion that neonatal interventricular haemorrhage may be associated with the use of oral beta-sympathomimetic drugs, although the data are preliminary. There have been only a few small studies of possible long-term ill effects

for the neonate, and currently it appears there is no difference in developmental outcome.

Prostaglandin synthetase inhibitors (NSAIDs) cross from the mother to the foetus, potentially resulting in prolonged bleeding time, cardiopulmonary effects like premature closure or constriction of the ductus arteriosus and persistent foetal circulation, renal dysfunction, and reduced urinary output. Necrotizing enterocolitis and neonatal intra-ventricular haemorrhage have also been recorded in association with the use of these agents. Most studies have limited the use of prostaglandin synthetase inhibitors to short-term therapy (48–72 hours) before 32 to 34 weeks gestation. Newer and possibly more specific prostaglandin synthetase inhibitors such as sulindac, ketorolac, and the COX-2selective agents (e.g., nimesulide) are considered to have fewer foetal side effects.

Magnesium sulfate also readily crosses the placenta and may compromise foetal cardiac activity, with reduced baseline variability of the foetal heart rate demonstrated by cardio tocography being a common association, which in turn may lead to unnecessary intervention. The neonate may exhibit hypotonia and hypocalcaemia as a consequence of the hypomagnesaemia. The more controversial aspects of magnesium sulfate are related to its possible foetal neuro protective role, as several

observational studies indicated a reduction in cerebral palsy rate in very low birth weight infants in association with its use.

Mitterdorf and associates,, have found in their small randomized controlled trial(MagNET trial) that there is a highly significant association between tocolytic magnesium sulfate exposure and total neonatal mortality rates and worse outcomes in relation to interventricular haemorrhage, periventricular leukomalacia, and cerebral palsy.

Crowther and associates (2003) presented the much larger ACTO MgSO4 trial and did not observe an increase in perinatal or neonatal mortality rate. A no significant reduction of adverse neurologic sequelae was reported.

Calcium-channel blockers have not been adequately evaluated with regard to foetal or neonatal effects, and the Cochrane reviewers recommended the assessment of different dose and formulations on maternal and neonatal outcomes. Some animal studies have demonstrated profound metabolic alterations in the foetus, but these changes have not been confirmed in the foetuses of pregnant women.

Newer tocolytic agents such as nitric oxide donors and oxytocin receptor antagonists have not been sufficiently assessed. The maternal

administration of thyrotropin-releasing hormone in association with corticosteroids was thought, from preliminary studies, to enhance the development of foet a llung maturity. The ACTOBAT Study demonstrated results to the contrary and hence, its use is discouraged.

Maternal corticosteroid administration to enhance foetal lung maturity is beneficial for the preterm neonate but may carry a number of risks, including infection, although the latest available data do not confirm this potential complication. These potential risks must be balanced against the proven beneficial effect on neonatal pulmonary function and the possible reduction in interventricular haemorrhage and necrotizing enterocolitis.

The Dutch trial which studied the effects of maternal prenatal corticosteroid administration, suggested a long-term increase in the incidence of pharyngeal and ear infections in infants of treated mothers but reported no clear evidence of significant foetal or neonatal infection in preterm labour associated with intact membranes. The former practice of repeated maternal corticosteroid administration encouraged by the NIH Consensus Statement (1994) for pregnancies at risk for preterm delivery between 24 and34 weeks' gestation is questionable. Crowley and associates, in their studies, suggested that there was little evidence of

adverse long-term outcomes with repeated maternal corticosteroid administration.

Walfisch and colleagues reviewed 280 articles on this topic and concluded that there are no well-designed randomized controlled trials (RCTs) in humans that support the advantages of multiple courses over a single course of antenatal corticosteroids.

They also commented that an increasing body of evidence raises the concern of adverse consequences from the use of repeated courses. This conclusion is consistent with the current Cochrane systematic review of three trials. However, fewer infants required surfactant and there were fewer cases of severe respiratory distress syndrome (RDS)

AIM OF THE STUDY

This study aims at evaluating phosphorylated cervical insulin like growth factor binding protein for the prediction of preterm delivery. This is a bed side test for detecting phosphorylated cervical insulin like growth factor binding protein from cervical secretion and its value in the prediction of preterm delivery.

MATERIALS AND METHODS

The study was conducted in the Dept. Of Obstetrics and Gynaecology in Stanley Medical College and Hospital, Chennai over a period of December 2013 to September 2014 after getting clearance from the ethical committee. The study is a prospective study involving 50 patients presenting to our hospital with symptoms of preterm labour. These included pregnant females with 28-36 weeks of gestation selected both outpatient department and casualty.

Inclusion Criteria

- Gestational age between 28-36 weeks
- Regular uterine contractions
- Intact membranes
- Cervical dilatation 1 to < 3 cm

Exclusion Criteria

- Pregnancy before 28 and after 37 weeks
- Premature rupture of membranes
- Bleeding per vagina
- if they had cervical encirclage
- had been on tocolysis at admission

- cervical dilatation of more than3 cm
- Multiple pregnancies
- Hypertensive disorders complicating pregnancy
- Heart disease complicating pregnancy
- Other maternal and fetal indications requiring termination of pregnancy such as intrauterine growth retardation, lethal congenital malformations, were also excluded from the study.

Detailed history and examination of all patients were done. Gestational age was calculated based on the last menstrual period and confirmed by first trimester or early second trimester ultrasonography. A detailed general systemic and obstetric examination including digital cervical assessment after performing the test was done in all cases.

Performing the Test

The bedside test kit for pIGFBP-1 is an immuno-enzymatic test using monoclonal antibody for detecting antibody specific for the phosphorylated form of IGFBP-1.

Specimen collection

After explaining the procedure to the patient and getting the consent patient is placed in the dorsal position .A sterile speculum is introduced into the vagina and the cervical os visualised. A sterile dacron

swab was applied over the cervical os and was left approximately for 10-15 seconds to absorb cervical secretion.

Extraction of specimen

The specimen was extracted from the swab by swirling the swab vigorously in the tube containing extraction solution for 5- 10 seconds.

Dipping

Aluminium foil pouch containing dipstick was opened and the yellow testing dip area of stick was placed into tube containing the sample and was held until the liquid entered the result area. Dipstick was removed from the solution and placed in horizontal position. Result was observed in 5 minutes.

Reading the Result

Positive: When two lines were visible.

Negative: When only one control line was visible.

Absence of distinct control line meant invalid result.

The test is based on immune-chromatographic qualitative analysis of cervical phosphorylated insulin-like growth factor binding proteın-1.

All cases were administered a course of corticosteroids to enhance foetal pulmonary maturation as well as tocolysis as per our departmental

protocol. All patients were followed up to delivery. Following delivery, data collection about admission to delivery interval was analysed.

TABLE: 1

TEST AT ADMISSION

TEST	NO. OF CASES	PERCENTAGE
POSITIVE	32	64%
NEGATIVE	18	36 %
TOTAL	**50**	**100 %**

Thirty two women (64%) tested positive for pIGFBP-1 while eighteen women (36%) tested negative.

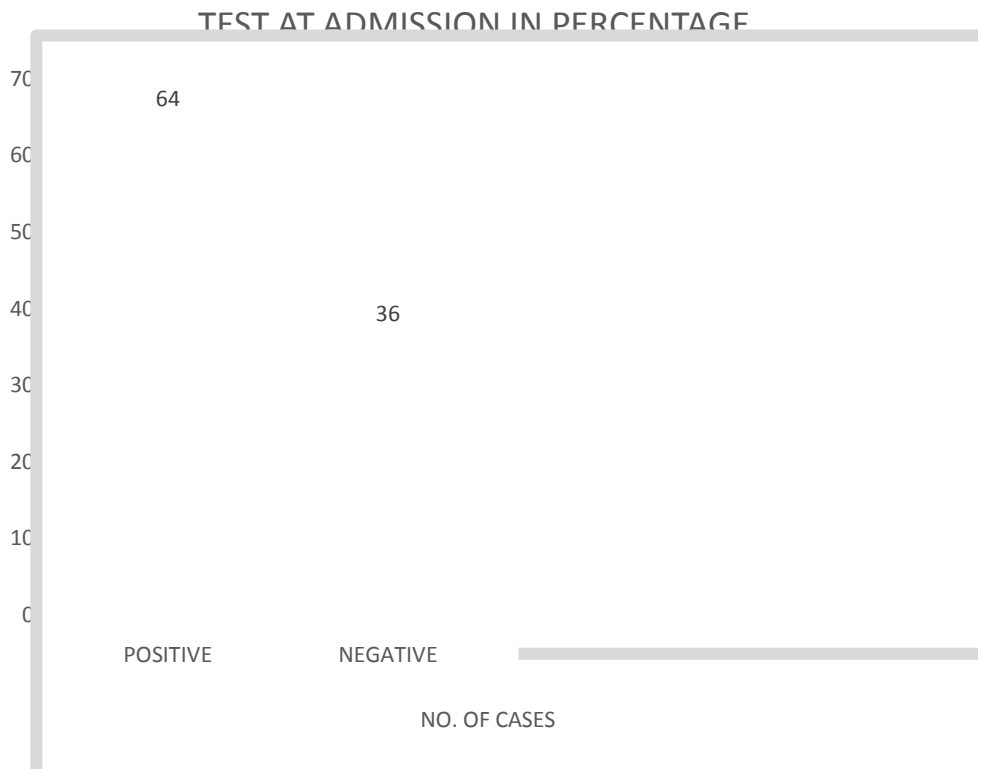

TEST AT ADMISSION IN PERCENTAGE
70
60
50
40
30
20
10
0
64
36
POSITIVE
NEGATIVE
NO. OF CASES

TABLE: 2

Test Result: Delivery Status Crosstabulation

			Delivery Status		Total	P value
			Delivered	Not Delivered		
Test Result	**Positive**	Count	30	2	32	<0.001**
		% within Test Result	93.8%	6.3%	100.0%	
		% within Delivery Status	93.8%	11.1%	64.0%	
	Negative	Count	2	16	18	
		% within Test Result	11.1%	88.9%	100.0%	
		% within Delivery Status	6.3%	88.9%	36.0%	
Total		Count	32	18	50	
		% within Test Result	64.0%	36.0%	100.0%	
		% within Delivery Status	100.0%	100.0%	100.0%	

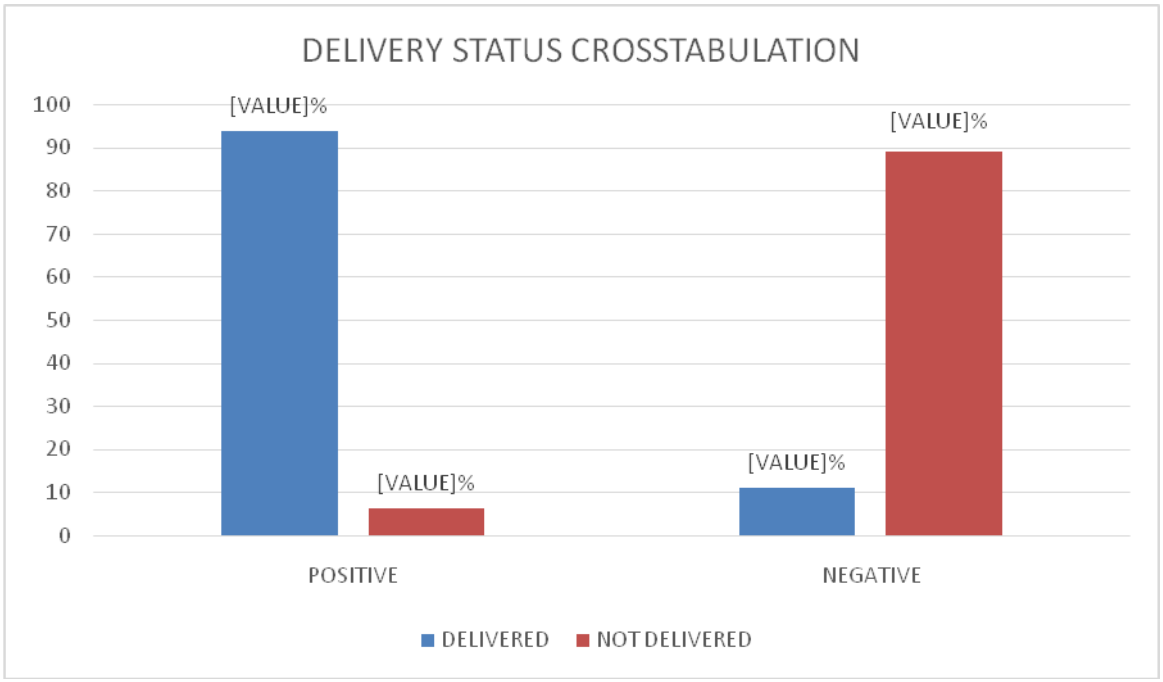

DELIVERY STATUS CROSSTABULATION
100
90
80
70
60
50
40
30
20
10
0
[VALUE]%
[VALUE]%
[VALUE]%
[VALUE]%
POSITIVE
NEGATIVE
DELIVERED
NOT DELIVERED

TABLE: 3

CORRELATION OF OBSTETRIC STATUS AND TEST

S.NO	OBST.CODE	DELIVERED/NOT DELIVERED	NO OF CASES	PERCENTAGE
1.	PRIMI +ve	DELIVERED	18	100%
		NOT DELIVERED	0	-
2.	PRIMI -ve	DELIVERED	0	-
		NOT DELIVERED	7	100%
3.	MULTI +ve	DELIVERED	12	85.71%
		NOT DELIVERED	2	14.29%
4.	MULTI -ve	DELIVERED	2	18.18%
		NOT DELIVERED	9	81.82%

Among the 18 primigravida patients with a positive test, all 18 delivered and the 7 primigravida women with a negative test, none of them delivered.

Among the 14 multigravida patients with a positive test, 12 delivered and the 11 multigravida women with a negative test, 2 of them delivered.

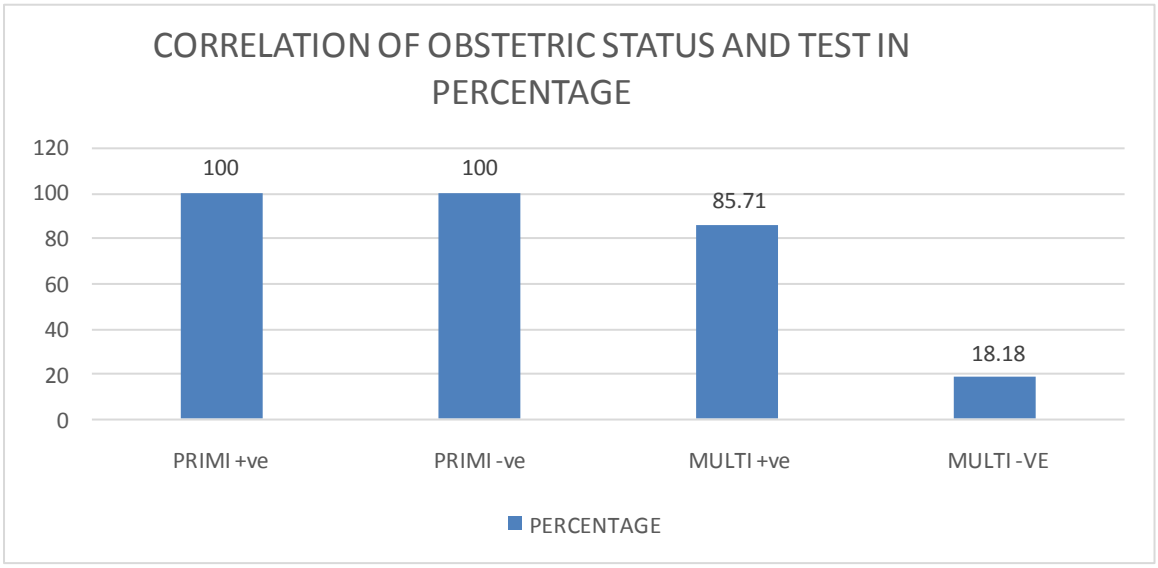

CORRELATION OF OBSTETRIC STATUS AND TEST IN PERCENTAGE
120
100
80
60
40
20
0
100
100
85.71
18.18
PRIMI +ve
PRIMI -ve
MULTI +ve
MULTI -VE
PERCENTAGE

TABLE: 4

CORRELATION OF CONTRACTIONS AND TEST

CONTRACTIONS	TESTS	TOTAL NO.	DELIVERED	NOT DELIVERED
2-3 CONTRACTIONS	POSITIVE	3	2	1
	NEGATIVE	18	2	16
3-4 CONTRACTIONS	POSITIVE	29	28	1
	NEGATIVE	–	–	–

TABLE: 5

CORRELATION CERVICAL DILATATION AND TEST

CERVICAL DILATATION	TESTS	TOTAL NO.	DELIVERED	NOT DELIVERED
1F	POSITIVE	14	14	-
	NEGATIVE	6	-	6
2cm	POSITIVE	18	16	2
	NEGATIVE	12	2	10

TABLE: 6

Correlation of Gestation Age and Test Result

PERIOD OF GESTATION IN WEEKS	POSITIVE		NEGATIVE	
	NO	PERCENTAGE	NO	PERCENTAGE
28-30	8	25.1	5	27.78
30-32	4	12.5	5	50
32-34	11	34.38	7	22.22
34-36	9	28.12	1	
TOTAL	**32**	**100**	**18**	**100**

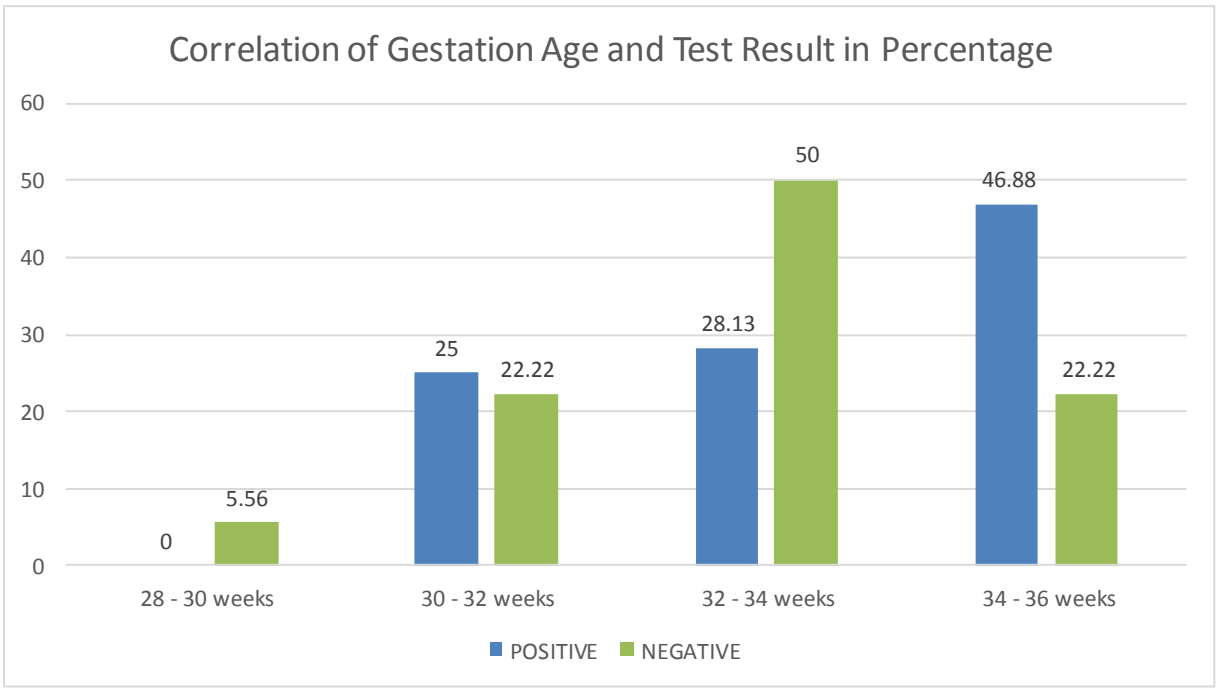

Correlation of Gestation Age and Test Result in Percentage
60
50
40
30
20
10
0
0
5.56
25
22.22
28.13
50
46.88
22.22
28 - 30 weeks
30 - 32 weeks
32 - 34 weeks
34 - 36 weeks
POSITIVE
NEGATIVE

TABLE: 7

CORRELATION OF TEST TO DELIVERY INTERVAL

(POSITIVE TEST)

TEST TO DELIVERY TIME INTERVAL	POSITIVE TEST	
	NO.	PERCENTAGE
<2 DAYS	19	63.34 %
2-7 DAYS	10	33.33%
>7 DAYS	1	03.33%
TOTAL	**30**	**100%**

In patients with positive test 19 delivered within 48 hrs, 10 delivered within 2-7 days and 1 delivered after 7 days.

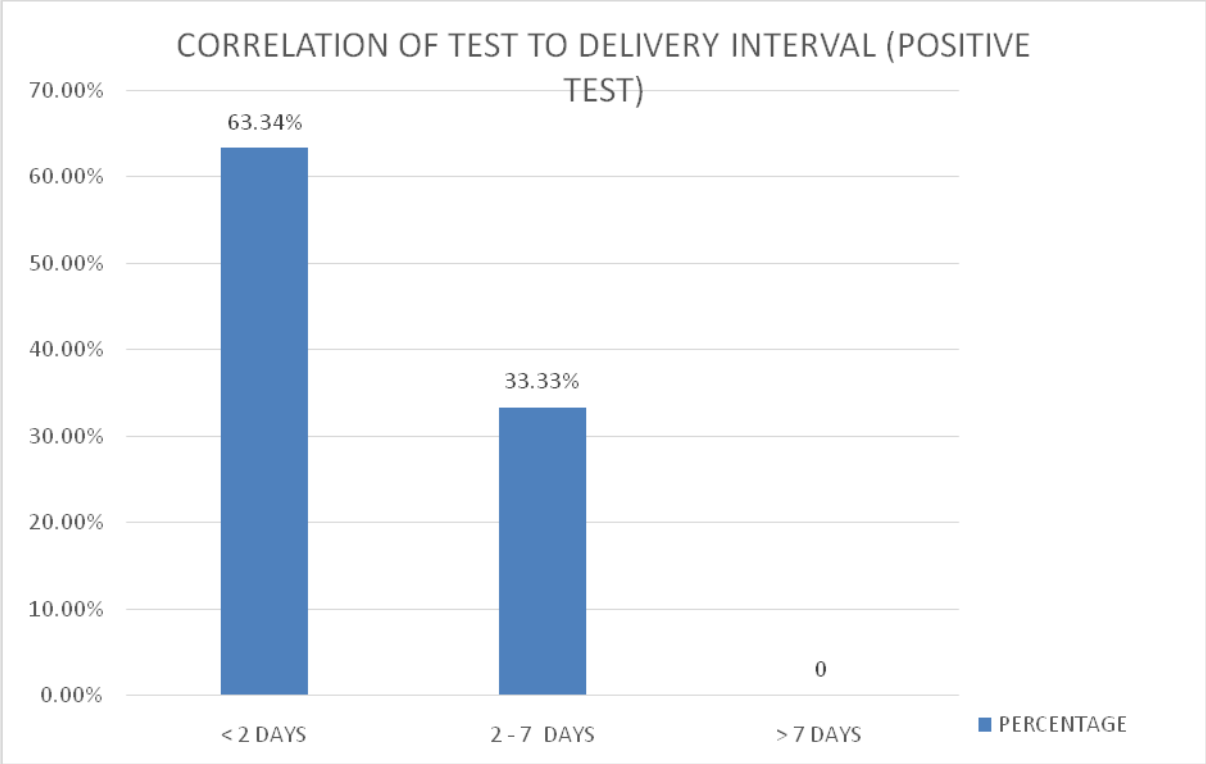

CORRELATION OF TEST TO DELIVERY INTERVAL (POSITIVE TEST)
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
63.34%
33.33%
0
< 2 DAYS
2 - 7 DAYS
> 7 DAYS
PERCENTAGE

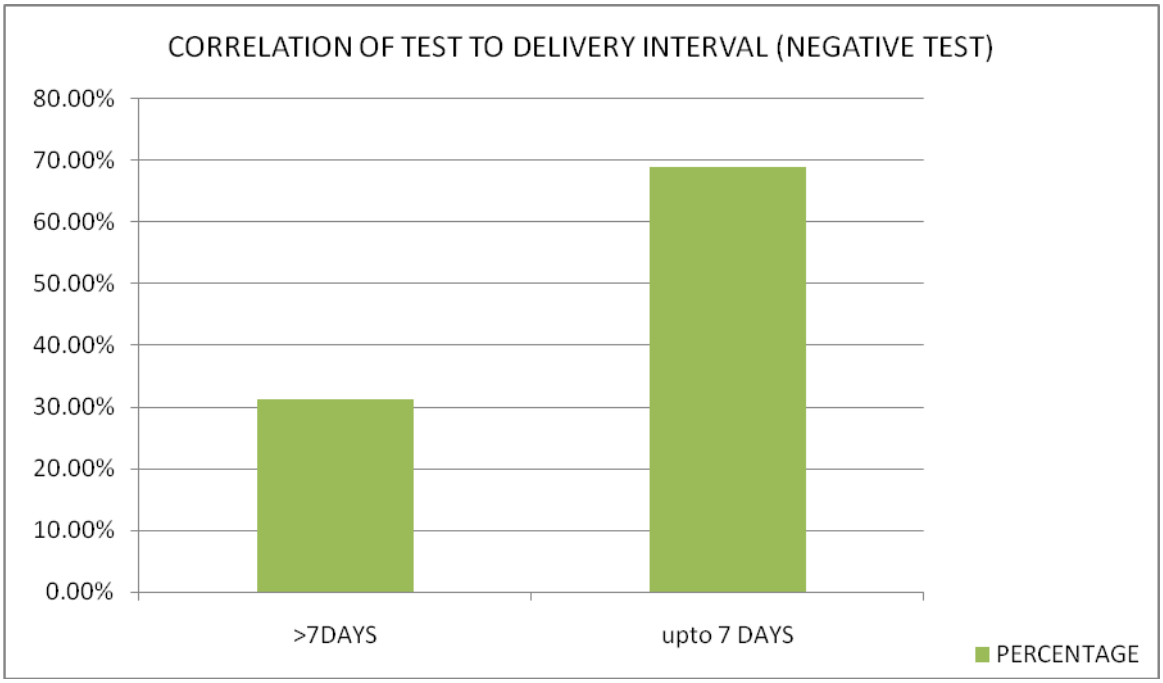
TABLE: 8

CORRELATION OF TEST TO DELIVERY INTERVAL

(NEGATIVE TEST)

TEST TO DELIVERY TIME INTERVAL	NEGATIVE TEST	
	NO.	PERCENTAGE
<7 DAYS	5	31.25 %
Up to 7 DAYS	11	68.75%
TOTAL	16	100%

In patients with negative test 11 patients did not deliver up to 7 days and 5 patients continued pregnancy beyond 7 days. Only two patients who had a negative test delivered prematurely.


CORRELATION OF TEST TO DELIVERY INTERVAL (NEGATIVE TEST)
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
>7DAYS
upto 7 DAYS
PERCENTAGE

RESULT

A total of 50 women were selected for the study. The range of gestational age was between 28 and 36 weeks. Thirty two women (64%) tested positive for pIGFBP-1 while eighteen women (36%) tested negative. All the patients received antenatal steroids and tocolytic therapy according to our hospital protocols.

Among the 32 patients with a positive test, only 2 delivered at term and the other 30 patients delivered preterm (<37 weeks). Among the 18 women with a negative test, only two delivered preterm.

Among the 18 primigravida patients with a positive test, all 18 delivered and the 7 primigravida women with a negative test, none of them delivered.

Among the 14 multigravida patients with a positive test, 12 delivered and the 11 multigravida women with a negative test, 2 of them delivered. In patients with positive test 19 delivered within 48 hrs, 10 delivered within 2-7 days and 1 delivered after 7 days.

In patients with negative test 11 patients did not deliver up to 7 days and 5 patients continued pregnancy beyond 7 days. Only two patients who had a negative test delivered prematurely.

DISCUSSION

Preterm delivery and birth remains a major concern of obstetric practice. It is the second leading cause of neonatal mortality and morbidity. Unfortunately, many tests are not available to diagnose preterm labour precisely. A physiologic marker for the onset of preterm birth is the presence and frequency of the uterine contractions and cervical dilatation. However, this finding alone is not predictive of preterm delivery. As the accurate diagnosis of preterm labour is not so simple many false-positive diagnosis have been made.

In our study 32 women (64%) tested positive for PIGFBP-1, while 18 women (36%) tested negative. Among the 32 patients with a positive test, only 2 delivered at term and the other 30 patients delivered preterm (<37 weeks). Among the 18 women with a negative test, only two delivered preterm ($p < 0.05$).

The positive predictive value of the test is 93.75% and the negative predictive value is 88.89%. The p value was <0.001.

The women who tested negative for IGFBP-1 had a significantly shorter stay in the hospital. The result shows that the bedside test for PIGFBP-1 has a sensitivity of 93.8% and a specificity of 88.9% for the prediction of preterm delivery before 36 weeks.

In the study rapid diagnostic test for prediction of preterm delivery by actimpartus kit in Department of Obstetrics and Gynaecology, Hi Tech Medical College, Utkal University, Bhubaneshwar, India 94 patients were recruited. Positive was 28 and negative was 60 .Admission to delivery interval in weeks was 2.3 and 5.1 respectively. The P value was <0.001 and significant.

In another prospective cohort study conducted in the Dept. of Obstetrics and Gynaecology, SN Medical College and Hospital, Agra, included pregnant females with 28-36 weeks of gestation .Fifty cases were included in this study. A positive result was associated with significantly reduced admission-to-delivery interval. The median admission-to-delivery interval was 3.25 days in the group with positive PIGFBP-1 results while 6.97 days with a negative PIGFBP-result ($p < 0.001$). Sensitivity, specificity, positive predictive value and negative predictive value of Actimpartus test is 72.22%, 90.6% 81.25% and 85.29%, respectively.

In studies of Kwek et al, 47 women suspected preterm labour between 23 and 33 weeks were taken and bedside test for IGFBP-1 was performed. Twenty-nine women (61.7%) tested negative and 18 women tested positive (38.3%). In addition, 91.7% of the patients in the IGFBP-1 negative group had a delay of more than 7 days between the onset of

contractions and delivery, while only 44.4% of the women in the pIGFBP-1 positive group experienced such a delay. The result shows that the bedside test for PIGFBP-1 has a sensitivity of 87.37% and a specificity of 82.6% for the prediction of preterm delivery before 36 weeks. The positive predictive value of the test is 77.8% and the negative predictive value is 79.2%.

In a study conducted by Elizur, et al, mean gestational age at delivery in patients testing positive for beside test for PIGFBP-1 was 36.2 ± 2.4 weeks (p value 0.001).

The result shows that bedside test for PIGFBP-1 has a sensitivity of 87.37% and a specificity of 82.6% for the prediction of preterm delivery before 36 weeks.

The positive predictive value of the test is 77.8% and the negative predictive value is 79.2%.

Lembet et al, conducted a prospective study on 36 women between 20 and 36 weeks of gestation with regular contractions. Eighteen patients had a positive beside test for PIGFBP-1 and 18 had a negative test. Among the 18 patients with a positive test, only one delivered at term and the other 17 patients delivered preterm (<37 weeks). Among the 18 women with a negative test, two delivered preterm ($p < 0.05$).

Sensitivity, specificity, positive and negative predictive values of the rapid PIGFBP-1 test for preterm delivery were 89.5%, 94.1%, 94.4% and 88.9%, respectively.

In study of Ting et al 108 patients were recruited into the study. Patients tested negative for PIGFBP-1, the median (± standard deviation [SD]) gestational age delivery was 37.4 weeks (± 1.8 weeks) and in positive PIGFBP-1 the median gestational age at delivery was 32.9 weeks (± 4.0 weeks). The p value was <0.001.

Based on this discussion it can be concluded that results are comparable for beside test for PIGFBP-1. This test has very reasonable accuracy and easy to use

SUMMARY

Preterm labour is a significant factor affecting perinatal outcomes, in terms of complications and mortality. Preterm labour is the onset of labour before 37 weeks of gestation birth.

About 40-45% of preterm labour occurs spontaneously and 30% because of rupture of membranes (preterm), and the rest 30-35% are induced preterm labours. Infection is one of the most common cause of preterm labour and responsible for 20-40% of all preterm cases. preterm labour is established when regular uterine contractions occur at least 4 in 20 minutes or 8 in 60 minutes with progressive change in cervical score with effacement 80% or more and dilatation more than 1 cm occurs. Preterm labour can be diagnosed by various factors .Preterm labour can be diagnosed by clinical methods and by investigations.

Diagnosis of preterm labour poses a major problem. Any test that can precisely diagnose preterm labour will be of much help. One of the latest modality in predicting preterm labour is phosphorylated insulin like growth factor binding protein -1 in cervical secretions. The maternal concentration of insulin like growth factor binding protein 1 increases as pregnancy advances and forms a major constituent of amniotic fluid from second trimester onwards.

During the process of labour, the choriodecidual interface is disrupted releasing the phosphorylated insulin like growth factor binding protein -1 into the cervical secretions. Bed side kits have been developed for the qualitative detection of phosphorylated insulin like growth factor binding protein -1 above 10mg/l.

Our study was a prospective study. A total of 50 women were selected for the study. Swabs were placed in the cervix and left for 5- 10 seconds in patients with preterm labour.The swab was placed into a diluent and shaken vigorously for 5-10 seconds. The dip stick provided in the kit was placed in the diluent till the diluent gets absorbed. The dip stick was placed horizontally on the table and observed for the results.

Test is based on immune chromatographic qualitative analysis of cervical phosphorylated insulin-like growth factor binding proteın-1.

If 2 lines appear the test was considered as positive and if single line appeared the test was considered as negative. Test positive and negative cases were followed up for 2 weeks whether patient delivered or not. All the patients received antenatal steroids and tocolytic therapy according to our hospital protocols

The range of gestational age was between 28 and 36 weeks. In our study 32 women (64%) tested positive for PIGFBP-1, while 18 women

(36%) tested negative. Among the 32 patients with a positive test, only 2 delivered at term and the other 30 patients delivered preterm (<37 weeks). Among the 18 women with a negative test, only two delivered preterm ($p < 0.05$).

The positive predictive value of the test is 93.75% and the negative predictive value is 88.89%. The p value was <0.001.

The women who tested negative for IGFBP-1 had a significantly shorter stay in the hospital. The result shows that the bedside test for PIGFBP-1 has a sensitivity of 93.8% and a specificity of 88.9% for the prediction of preterm delivery before 36 weeks.

CONCLUSION

Cervical phosphorylated insulin like growth factor binding protein -1 alone is a useful tool for predicting women who are at risk for pre-term delivery. It is a rapid bedside immune enzymatic test. It is an easy, lucid, faster, convenient method of predicting preterm labour and exclusion of premature labour and delivery in symptomatic women. The test is easy one step rapid dip stick test and can be done by any health worker clinicians, nurses, or laboratory technicians in both urban and rural settings and does not need expertise opinion.

It is less expensive. With symptomatic patients a negative test result is a clear indication that the delivery will not start within the next 7 days. Cervical phosphorylated insulin like growth factor binding protein -1 has a higher negative predictive value of 1 in predicting risk of delivery within 48 hrs. If facilities available, this can be combined with measurement of cervical length and this will further increase the predictive value in predicting pre-term delivery in symptomatic women.

It will allow us to focus on women who are more likely to deliver preterm and timely in utero referral to higher centres equipped with

neonatal resusitation and preterm care. It also helps us avoid unnecessary referral and treatment and to curtail health care burden and costs.

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PROFORMA

DATE:

NAME: AGE: LMP:

IP NO: EDD:

D.O.A: D.O.D

OBSTETRIC CODE:

ADDRESS :

PRESENTING COMPLAINTS:

MENSTRUAL HISTORY : MD SINCE:

OBSTETRIC HISTORY:

PAST HISTORY:

GENERAL EXAMINATION:

HT: WT: TEMP: PR: BP:

PALLOR: PEDAL EDEMA:

CVS: RS:

P/A: CONTRACTIONS:

P/V:

INVESTIGATIONS:

HB: RBS: U/A:

USG:

CERVICAL SWAB TEST :

TREATMENT:

STAY IN HOSPITAL:

OUTCOME:

RESULT:

CONSENT FORM

I agree to participate in the study entitled ‘EVALUATION OF PREDICTION OF PRETERM LABOUR USING CERVICAL PHOSPHORYLATED INSULIN LIKE GROWTH FACTOR BINDING PROTEIN”

I confirm that I have been told about this study in my mother tongue and have had the opportunity to clarify my doubts.

I understand that my participation is voluntary and I may refuse to participate at any time without giving any reasons and without affecting my benefits.

I agree not to restrict the use of any data or results that arise from this study.

Name of the participant:

Sign / Thumb print:

Sign of Investigator:

NO.	NAME	AGE	OBST.Code	GA	CONT	CERV. DIL	D.O.T	+/-	DEL	DELIVERY INTERVAL	Delivery interval	ND for
1	Kasturi	21	P	32 weeks	2-3	1f	01.05.14	+ve	D	2 days	2-7 days	-
2	Padmini	22	G2A1	35 weeks	3-4	2cm	03.05.14	+ve	D	5 days	2-7 days	-
3.	Veni	18	P	34 weeks	2-3	1f	15.05.14	-ve	ND	Upto 7 days	-	Upto7
4.	Anandhi	30	G3A2	34 weeks	3-4	2cm	20.05.14	+ve	D	Leass than 2 days	Less than 2 days	-
5.	Kaveri	34	P	33 weeks	3-4	1f	30.05.14	+ve	D	2 days	2-7 days	-
6.	Felomina	25	P	34 weeks	3-4	1f	05.06.14	+ve	D	Less than 2 days	Less than 2 days	-
7.	Deepika	23	G2P1L1	33weeks	3-4	2cm	06.06.14	+ve	D	less than 2 days	Less than 2 days	-
8.	Easwari	29	G2A1	32 weeks	3-4	2cm	20.06.14	+ve	D	3 days	2-7 days	-
9.	Bommi	19	G2P1L1	34 weeks	2-3	2cm	30.06.14	-ve	ND	Upto 9 days	-	> 7 days

NO.	NAME	AGE	OBST.Code	GA	CONT	CERV. DIL	D.O.T	+/-	DEL	DELIVERY INTERVAL	Delivery interval	ND for
10.	Deepa	32	G2P1L1	30 weeks	3-4	1f	01.07.14	+ve	D	3 days	2-7 days	-
11.	Selvi	18	P	34 weeks	3-4	1f	01.07.14	+ve	D	less than 2 days	Less than 2 days	-
12.	Jameema	20	P	36 weeks	3-4	2cm	01.07.14	+ve	D	8 days	> 7 days	-
13.	Kumari	19	P	34 weeks	2-3	2cm	07.07.14	-ve	ND	Upto 7 days	-	Upto7
14.	Vaishnavi	18	G2P1L1	29 weeks	3-4	2cm	18.07.14	+ve	D	less than 2 days	Less than 2 days	-
15.	Sindhu	22	P	28 weeks	2-3	1f	20.07.14	-ve	ND	Upto 10 days	-	> 7 days
16.	Kiruthika	25	G2P1L1	31 weeks	3-4	2cm	22.07.14	+ve	D	4days	2-7 days	-
17.	Priya	24	G2A1	32 weeks	2-3	2cm	28.07.14	-ve	D	Upto 7 days	-	Upto7
18.	Kalpana	29	P	33 weeks	3-4	1f	29.07.14	+ve	D	less than 2 days	Less than 2 days	-

NO.	NAME	AGE	OBST.Code	GA	CONT	CERV. DIL	D.O.T	+/-	DEL	DELIVERY INTERVAL	Delivery interval	ND for
19.	Saraswathi	31	P	28 weeks	3-4	2cm	30.07.14	+ve	D	Less than 2 days	Less than 2 days	-
20.	Aparna	19	P	34 weeks	2-3	2cm	30.07.14	+ve	D	7days	2-7 days	-
21.	Valaikodi	24	G2P1L1	35 weeks	3-4	2cm	31.07.14	+ve	D	less than 2 days	Less than 2 days	-
22.	Fathima	27	P	28 weeks	3-4	1f	01.08.14	+ve	D	less than 2 days	Less than 2 days	-
23.	Archana	25	P	33 weeks	2-3	1f	01.08.14	-ve	ND	Upto 12 days	-	> 7 days
24.	Devi	30	G2A1	33weeks	3-4	2cm	14.08.14	+ve	D	less than 2 days	Less than 2 days	-
25.	Pushpavathi	33	P	35weeks	3-4	1f	14.08.14	+ve	D	4 days	2-7 days	-
26.	Nazia	22	P	36weeks	3-4	2cm	14.08.14	+ve	D	2 days	2-7 days	-
27.	Meera	21	G2A1	30 weeks	2-3	2cm	14.08.14	-ve	ND	Upto 7 days	-	Upto7

NO.	NAME	AGE	OBST.Code	GA	CONT	CERV. DIL	D.O.T	+/-	DEL	DELIVERY INTERVAL	Delivery interval	ND for
28.	Karthika	27	P	35 weeks	3-4	1f	14.08.14	+ve	D	less than 2 days	Less than 2 days	-
29.	Malar	30	P	34 weeks	3-4	1f	15.08.14	+ve	D	less than 2 days	Less than 2 days	-
30.	Yamuna	18	G2A1	31 weeks	2-3	2cm	16.08.14	-ve	D	Upto 7 days	-	Upto7
31.	Jayanthi	18	P	28 weeks	2-3	1f	16.08.14	-ve	ND	Upto 7 days	-	Upto7
32.	UshaNandhini	25	G3P2L1	34 weeks	3-4	1f	17.08.14	+ve	D	less than 2 days	Less than 2 days	-
33.	Nandhini	22	P	36 weeks	3-4	2cm	17.08.14	+ve	D	less than 2 days	Less than 2 days	-
34.	Banupriya	22	G3A2	32weeks	2-3	2cm	20.08.14	-ve	ND	Upto 7 days	-	Upto7
35.	Bagyalakshmi	23	G2P1L1	33 weeks	2-3	2cm	20.08.14	-ve	ND	Upto 7 days	-	Upto7
36.	Swati	25	P	29 weeks	3-4	1f	24.08.14	+ve	D	less than 2 days	Less than 2 days	-

NO.	NAME	AGE	OBST.Code	GA	CONT	CERV. DIL	D.O.T	+/-	DEL	DELIVERY INTERVAL	Delivery interval	ND for
37.	Kousalya	21	G2A1	36 weeks	2-3	2cm	25.08.14	+ve	ND	Upto 14 days	-	> 7 days
38.	Sangeetha	18	P	31 weeks	2-3	1f	25.08.14	-ve	ND	Upto 7 days	-	Upto7
39.	Lalitha	28	G2P1L1	33 weeks	2-3	2cm	27.08.14	-ve	ND	Upto 7 days	-	Upto7
40.	Pushpa	24	P	32 weeks	3-4	1f	28.08.14	+ve	D	less than 2 days	Less than 2 days	-
41.	Prema	29	G2A1	28 weeks	2-3	2cm	30.08.14	-ve	ND	Upto 8 days	-	> 7 days
42.	Sugumary	24	G3A2	35 weeks	3-4	2cm	01.09.14	+ve	D	less than 2 days	Less than 2 days	-
43.	Geetha	25	P	28 weeks	3-4	1f	01.09.14	+ve	D	3 days	2-7 days	-
44.	Rama Shankari	30	G2P1L1	33 weeks	2-3	2cm	03.09.14	-ve	ND	Upto 7 days	-	Upto7
45.	Usha	18	G3A2	29 weeks	2-3	2cm	03.09.14	-ve	ND	Upto 12 days	-	> 7 days

NO.	NAME	AGE	OBST.Code	GA	CONT	CERV. DIL	D.O.T	+/-	DEL	DELIVERY INTERVAL	Delivery interval	ND for
46.	Latha	29	G3A2	29 weeks	3-4	2cm	03.09.14	+ve	D	less than 2 days	Less than 2 days	-
47.	Renuka	23	G2A1	33 weeks	3-4	2cm	03.09.14	+ve	ND	Upto 7 days	-	Upto7
48.	Indra	22	G2P1L1	35 weeks	2-3	2cm	0409.14	-ve	ND	Upto 7 days	-	Upto7
49.	Gomathy	19	P	32 weeks	2-3	1f	04.09.14	-ve	ND	Upto 7 days	-	Upto7
50.	Jamuna	31	P	30 weeks	3-4	2cm	05.09.14	+ve	D	less than 2 days	Less than 2 days	-

Abbreviations:

Obst.Code: Obstetric Code**D.O.T**: Date of

GA: Gestational Age**Del**: Delivery Status

Cont: Contractions**ND for**: Not Delivered for

Cerv.Dil: Cervical Dilation

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Prediction of preterm labour using cervical Phosphrylated insulin like growth factor binding protein.

Principal Investigator : Dr. Vidhya Jayashree.K

Designation : PG in MS (O&G)

Department : Department of O&G
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 02.07.2014 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI